Royal Society of Medicine

President The Rt Hon Lord Adrian OM MD FRS

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Nuffield Lecture

The Evolution of the Teaching-hospital Physician in our Time

by Sir Francis Walshe OBE MD FRS (*London*)

My first duty is to express to the President and Officers of the Society my deep appreciation of the honour they have done me in inviting me to give the second Nuffield Lecture.

By way of preliminary I may remind you that the Nuffield Lecture has something in common with another distinguished lectureship within the gift of this Society; namely the Hughlings Jackson Lecture, in that both were founded within the lives of the men they are intended to honour.

In different ways, both men have served medicine greatly and have laid us and our successors under a heavy debt of obligation to them, for while Jackson was one of the deepest thinkers in medicine of the nineteenth century, Lord Nuffield has by his unexampled generosity and humanity made it possible for other seekers after knowledge within the field of medicine and its related activities, not only to add to knowledge but also to apply its fruits for the benefit of humanity.

These two themes, discovery and the enlightened patronage and support of discovery, deal with means to an end, and are not ends in themselves.

As Newman in his famous discourses on the nature of university education reminded us a century ago, the profession of medicine is not a liberal, but a practical one: that is, it is not followed for its intrinsic interest but for an end beyond this.

Thus, what I am proposing to consider this afternoon is one of the means by which this end – the prevention and cure of disease – is sought, namely, the physician himself.

So diversified is the field of medicine and its associated activities – preventive and curative medicine, medicine in the ward and in the laboratory, administrative medicine and the rest – that this choice of a single agent is imposed upon me.

To-day every kind of doctor, whether he admits it or not, is in some degree a specialist. At one extreme we have the general practitioner who is uniquely plunged in the tides of human lives, and at the other extreme, perhaps, the medical statistician who, by contrast, works in an almost Olympian remoteness from the human material of his studies. Indeed, in this respect his papers often remind me of the title of Thomas Gray's 'Ode on a distant prospect of Eton College'. For like the poet, in this if in nothing else, the statistician gazes from afar upon us and our weaknesses, genetic and acquired, perhaps even murmuring to himself as he does so, the well-known lines of the ode:

> 'Alas, regardless of their doom,
> The little victims play.
> No sense have they of ills to come,
> Nor care beyond today.'

and then turns back to his graphs and his statistical significances.

Somewhere between these extremes we find the physician, and it is of his development in the past fifty years, as I have watched it, and in a small way participated in it, that I shall speak. Indeed, one can reflect only upon one's own experience, and it has been said that 'a man who has never reflected upon the principles of his work has not achieved a grown-up attitude towards it. A scientist who has never philosophized about his science can never be more than an imitative journeyman scientist'.

To be more precise, the order of experience upon which I shall reflect is that of the physician attached to a teaching hospital. The topic may seem too narrow for such an occasion as this, but I remind you that amongst physicians he carries a great number of serious responsibilities: namely his part in the training of doctors and in setting an example of practice, in advancing knowledge, and in himself practising medicine, which still for the majority of his kind, involves private as well as hospital practice.

Those who were the clinical teachers of my youth, and later my senior colleagues, did fulfil these diverse roles and helped to form our traditions of practice, teaching and research. They gave us not only our vocational training, but also made major advances in knowledge. Their influence has been particularly lasting in the tradition of thorough clinical training which still lives and is a vital element in that insistence on first things first which has characterized British medicine. That first thing is the direct approach, the clinical assessment based upon history taking and physical examination. It was to this that Flexner in his well-known monograph on 'Medical Education' published in 1925, referred on his opening page as 'that kind of sagacious observation which is the stuff out of which science is ultimately made'.

Two Categories of Physician

I turn, then, to the changes which have marked the evolution of the physician in the last fifty years, and have given us to-day two categories of teaching hospital physician: the part-time consultant also engaged in private practice, and the professorial unit with its professor and assistants who work wholly within the hospital and its medical school.

We can agree, perhaps, more easily now than in 1920 when the units were first founded in this country, that the clinicopathological discipline which was the mainstay of my predecessors in medicine was becoming manifestly and progressively less adequate to cope with the problems of medicine, and that the methods and ideas of the physical and biological sciences were becoming increasingly essential to unravel the ætiology and the processes of diseases, so that to-day there is scarcely a single field of natural science that does not contribute to medicine, who, if I may personify her, was once the mother and the nurse of science.

Thus, it became clear that the structure of medicine and the demands of research could no longer be borne by the clinical staffs of the teaching hospitals as we had known them. Each increase in knowledge and in method complicated, not only clinical medicine as we practised it, but also the training of the doctors of the future. The formation of the professorial medical unit became an evident necessity, if a university standard of education was to be maintained, as the most far-seeing physicians have always desired it to be.

What was hoped for from this new element in the teaching hospital? It was accepted that in the final stages of preparing the medical student for the practice of medicine, the practising physician remained an essential teacher. His main work was not primarily to discover, but to inculcate established arts and techniques of medicine, and to humanize medicine: work which was of necessity largely repetitive, but required skill and ripe experience, though not altogether or even predominantly of a scientific nature. I speak now, be it remembered, of forty years ago.

On the other hand, it was intended that the professor and his assistants should be what James Paget, and following him, Thomas Lewis, had called clinical scientists. That is, it was their role to advance medical knowledge and to bring to their work all the scientific disciplines that were relevant to this task. Necessarily, their work began with the patient and ended with him in so far as he provided the material of their labours.

The professor was designed to engage in research in some chosen field, to train assistants in clinical science, and in his undergraduate teaching to expound the principles of medicine, to arouse in his students an interest in its purely scientific aspects, and to lead them to the critical study of what they saw, what they read and what they were taught. In short, to fit them to reach the frontiers of the known, and even to extend these if later it was in them to do so.

All these designs and aspirations may be found expressed in Flexner's monograph to which I have referred, and also in the several lectures and addresses which Thomas Lewis gave during the 'twenties and 'thirties.

Time has indicated that Lewis's concept of clinical science must now be widened, and in one of his last papers the late James Spence of Newcastle amplified this concept in discerning fashion (1954).

After forty years of usually peaceful co existence between these categories of physician, it is interesting to see how far the ideals of those who founded our professorial medical Units have been realized, and what effect their being has had upon the part-time consultant.

The Wandering Symposiast

Of course, things rarely work out according to plan. In the main the part-time physician has continued his former role, but has perhaps of late years tended to drop out of the stream of active research, not wholly, but more than is favourable for his future prospects.

The clinical professor and his whole-time assistants have not developed quite uniformly. This is specially true of the professor himself, who has sometimes found himself expected to take the lion's share of organizing the teaching in his hospital, or who, being possessed by an administrative urge, has taken it upon himself to do so.

This task has become progressively more exacting. It spawns committees and subcommittees with the fertility of a herring, and may take as

much of the professor's time and energy as the private practice of the part-time consultant was sometimes said to do – though the professor's time-table is the more predictable.

Nor can we turn a blind eye to the growing fashion of international symposia and congresses, with their social accompaniments, which involve recurrent distractions in the life of the professor and may tempt him to the periodical desertion of his chair. The wandering symposiast, who, to be accurate, is as often the part-time hospital physician as the professor, is a new phenomenon in our time, and I sometimes wonder whether his journeys are really necessary. In strict moderation these functions have their value, but as a habit they are adverse to systematic work. Only the small carefully selected symposium evokes the flow of reason. The rest are, for the most part, reiterations of matters already published.

Thus, beset by conflicting claims and responsibilities, the clinical professor has not been invariably able to carry out what was to have been his primary role; that of engaging in and encouraging research.

It is true that the special research units which have been set up by the Medical Research Council do, when they are situated in the teaching hospital, keep alive the atmosphere of research, but they do not unburden the professor of his administrative and other activities.

A cynic has said that the part-time hospital physician is one who spends part of his time in his hospital, but I feel that this qualification does no longer always suffice to distinguish him from his academic colleague.

If, then, the clinical professor is not invariably in a scientific heaven, how remote is he from the solid earth which his part-time colleague so perseveringly treads?

I should like to elaborate this contrast for a few moments, for it is not without significance to my theme.

Physicians and Patients

The physician, of course, is not the court of first instance in the bringing of medical knowledge and care to the sick. This court is constituted by the general practitioner who rightly insists upon his prerogative in this respect, yielding it willingly only when he is himself the patient.

Yet the physician, when he meets his patient, does so alone. He has to listen to his story patiently and with evident interest. No satisfactory relationship is established between the private physician and the patient unless this requirement is met. It may involve listening to an authorized and to a revised version of the history, and my own experience is that wives are the most prolific authors of revised versions, for the really good wife is always sure that her husband does not really know what his symptoms are and what they are all about. I have to admit that not seldom she is the more reliable witness – but I refrain from any generalization.

Having accomplished this important business of history taking and completed his physical inquisition, the private physician is expected forthwith to announce some plan of action, and to commit himself to some opinion, however provisional it may be at this stage.

Moreover, if manifold investigations are called for, his patient expects to be given a glimpse of the programme, as it were, to be told something of the plot and of what denouement may be hoped for. No houseman or registrar stands between the physician and the need to meet directly and at once the emotional urgency of the situation as the patient and his family may see it.

In contrast, the approach of the clinical professor is more impersonal and is usually public, in the ward.

The patient's history has already been taken by the houseman and probably edited by a registrar, and has lost any spontaneity it may once have had. Like the patient himself, it has been tidied up, and none of those unpremeditated parentheses which occasionally illuminate and clarify the situation is likely to be uttered. The patient may then easily find himself already upon the diagnostic conveyor belt, moving from department to department, from expert to expert, with little or no clue as to what it is all about, and with no obviously designated person whom he can ask. In fact, no one is specially charged to tell him, and what is everybody's business may easily become nobody's business. At worst, if his professor is concentrating upon some special state of disease, the patient may drop back into the role of being the medium of some pathological process or syndrome, or a twig on a pedigree, with no identity as a human person.

Finally, our academic physician as he stands brooding by the ward bedside, has a subsidiary awareness that he is not going to be asked in a few minutes to descend to a family living room, to face the family group or clan, to give a firm decision, a plan of action, or a diagnosis, or, *horribile dictu!* to stand cross-examination by them. A houseman, or a registrar stands between him and the domestic and diplomatic aspects of the practice of medicine, important though these be.

Let me be clear that all this is not a criticism, but an endeavour to give a candid account of the contrasts between institutional and private clinical medicine as they are almost of necessity practised by the physician in these different

circumstances, and – let us not forget it – as they are experienced by the patient.

How many of my professorial brethren will recognize themselves and their situation in this hasty thumbnail sketch, of course I cannot say. I must admit that even the most distinguished artist may paint a portrait in which the sitter cannot easily recognize himself, when for the first time – often an unnerving moment – he is allowed to see the canvas, but at least he knows how he has appeared to one earnest and unprejudiced observer.

You may well think that I have drawn too hard an antithesis between the academic and the practising physician. Perhaps it is too starkly drawn, for after all, the clinical scientist can find his problems only from the study and care of sick persons, and he must have the clinical experience to see these problems when they present. Moreover, it is in his hands to see that clinical science is not a dehumanized medicine, as indeed within my experience it usually is not.

Nevertheless my contrast is not without a significant reality.

Physicians and Research

Thus, if there is not an identity of experience between clinical scientist and practising clinician, there is at least an overlap, and it is to the other aspect of this overlap that I now turn, namely, the matter of original contributions.

Is it reasonable to expect the part-time hospital physician to engage in original research, and if so, of what order? Is it more difficult for him to do so than for his academic colleagues?

In the days before the coming of the National Health Service when the young teaching-hospital physician was wholly dependent upon private practice for his living and not largely independent of it, he had in many cases to take up appointments in small outlying hospitals which would bring him into relation with local general practitioners who, he hoped, would be a source of private patients for him. Thus at the naturally most productive period of his life he was often debarred or obstructed by too many routine activities to engage in any original work.

Nevertheless, as anyone familiar with the history of medicine in this country for the past hundred years will know, teaching-hospital physicians did undertake wholly unsubsidized research, in many instances with great distinction. After all, who else was there to do it?

I find it difficult to believe that a physician with consultant status on the staff of a teaching hospital can at this date plead these embarrassments which beset, but did not always defeat, his predecessors. He is surely free to devote some time to making at least some modest contribution to the advancement of medical knowledge if it is in him to do so, and he feels a responsibility in the matter.

At this point in any candid discussion of the subject we have to accept that many able and experienced physicians have no interest beyond the practice and teaching of medicine as they find it, and that some have never entertained an original idea in their professional lives, or noted a clinical phenomenon that was not already on record.

To force them to go through the motions of research would be absurd, and would distract them from the optimum use of the gifts they have, and these may be rich.

Nevertheless, in a university school of medicine the ideal is that every teacher is a learner, and every learner must in the nature of things be a seeker. Were medicine wholly scientific there would be no room for anyone who was not a seeker for the new and undiscovered, but where so much remains that is art rather than science, and insight into human beings rather than originality, the artist and the humanist in medicine still has his place, though the unceasing utilization of scientific means and ideas in medicine somewhat narrows his scope and makes his future not altogether clear.

I make this last comment, not because I wish to see the disappearance from our scene of the pure practising clinician, for his place is as important as ever, but by way of suggesting that the preservation in our educational scheme of a proportion of part-time physicians requires that some amongst them must do what their predecessors found it possible, under harder circumstances, to do; namely, to regard the advancement of knowledge as being amongst their responsibilities.

Perhaps, then, we should be reluctant too readily to absolve candidates for a place on the staff of a teaching hospital from some sense of responsibility to add to the store of new knowledge while they are still young enough to do so. It is possible to have too large a proportion of physicians and teachers who are content to move incuriously through life upon the permanent way of established knowledge and procedures, simply adding to their personal experience within these limits.

The Training of the Physician for Research

So far I have spoken as though nothing more were needed for the physician to undertake research in clinical science than a natural gift for this activity and a desire to engage in it. I have said nothing about his training to this end, and the moment has come to ask whether there is a role in research for the young graduate in medicine who has had no special training beyond that of the normal curriculum, and the often fortuit-

ously chosen postgraduate clinical appointments he has to serve in before and after registration.

If medicine were a clearly defined and restricted scientific discipline, like chemistry or botany, we might expect this experience spread over seven years to be adequate enough, but we know the width and diversity of the subjects to be covered in a medical education, and the corresponding lack of depth which this range of subjects necessarily implies.

Therefore, it seems clear that something more, and something more clearly defined and restricted, must be as essential to the training of the clinical scientist, as to a would-be scientist in any discipline of physical or biological science. This seems to me to be a problem that we have never corporately faced, and to it I will later return.

In the meantime, I feel sure that there is a role in original observation for the graduate without this special training, even though it be restricted in scope. A century or so ago Claude Bernard assured his contemporaries that clinicopathological studies were played out as a source of knowledge, and that they should leave the wards for the laboratory where alone could fundamental knowledge be gained. Somewhat intimidated by this dictum, clinicians from time to time have been prone to repeat it.

I believe this obituary of the clinicopathological method to be as premature now as when Bernard first uttered it. New entities are continually being identified, and for those who will pick me up on the use of this word 'entity', I will remind them that an entity is anything we can think about, and that I am not hypostatizing the concept of disease.

To take but a single example within my own field of interest, recent clinical and pathological studies of cerebrovascular disease have profoundly altered our ideas on this subject. They have revealed that the arteries tributary to the brain that lie in the neck, the internal carotid and cerebral arteries, play as important a role in cerebrovascular accidents as do the vessels entering into and issuing from the circle of Willis. Hitherto, the neck had always been a no-man's-land for the morbid anatomist making autopsies on persons dead of cerebral vascular accidents, and atheromatous changes in these two large extracranial vessels were not looked for, or not attended to, until very recently.

We now know that the state of the cerebral circulation is as determined by the state of these vessels as by that of the intracranial arteries. Comparably, in every field of medicine, new clinicopathological entities are being exposed, not because they are newly happening, but only because they are newly observed.

Therefore, for the trained senses of the alert clinical observer there remains, I believe, much of importance yet to be discovered.

What we need is the retention into adult life of the eager natural curiosity of the child, perfected by training and by exercise, respected for the prime gift it is, and kept alive by a constant awareness of the great gaps in our knowledge of illnesses and the grave limitations in our power to prevent and to cure them.

Yet wider goals can be achieved by this trained alertness. It makes possible those planned studies of diseases which we have not adequately made in the past, and is the foundation of clinical trials.

Nevertheless, when we have said all that can be said in this regard, we have to admit that we cannot, in most instances, hope to carry our problems of the ætiology and pathogenesis of disease to a final conclusion without the application of the physical and biological sciences. Therefore, we may not echo the call of Bernard to desert the ward for the laboratory. We must continue to retain the old lamps of clinicopathological study while getting what extra light we need from the new lamps of modern science.

Yet is the physician to cease to follow up his original observations at the point where these need to be carried to the laboratory for further analysis? Is he then to hand his problem over to the medically untrained scientist? If he has no special training in science he may have to do so, but ideally this should not have to happen. Too many medical problems have disappeared into the laboratory, finally emerging in a guise unrelated to the realities of the disease being studied.

Thirty years ago Wilfred Trotter reminded us in these words that 'medicine more and more understanding the lost opportunities of the past will take to itself the methods of the experimental sciences and lead the direct attack upon its own problems'.

This, I submit, should be taken to apply as much to the part-time teaching-hospital physician as to his academic colleague, and in a rapidly changing profession, he will with difficulty, if at all, retain an equality with the professor and his assistants, or even his place in the scheme of medical education, unless he takes his part in this direct attack. There are forces at work favouring his ultimate elimination. He has to justify himself on both the vocational and the scientific fronts if he is to survive. I see no reason in the nature of things why he should not do so.

We have to accept, therefore, that when planned surveys of disease, epidemiological and statistical studies, genetics and the classical clinicopathological approach have told us all they can, there remains the necessary experimental method still

to be pursued, and this involves the application of many physical and biological sciences.

Experimental Research

Over and above his purely medical experience, no one can achieve a true competence in more than one or two of these other disciplines: physics, chemistry, biochemistry, immunology and the rest. Since many unsolved riddles in neuropathology, for example, as in other aspects of pathology, require the knowledge and utilization of several scientific disciplines for their solution, it is clear that small carefully chosen teams of different workers must often collaborate. One or more of these must be medically trained and of sufficient competence in scientific method to command the respect of his non-medical colleagues, and to keep the medical view and aims of the research in sight. It is unreasonable to expect non-medical scientists to be interested in and to undertake alone fragmentary aspects of a complex medical research programme, and to treat them as technicians without exposing the problem to them in its fullness, as far as this can be seen.

I will not repeat in any detail what I have said on a number of occasions in the past twenty-five years, that the history of research into the disease beri-beri is a typical example of how the advance of knowledge may be delayed when there is a lack of communication and of a common ground of knowledge between those who are attacking the problem from different points of approach.

The remarkable, but forgotten, clinical, pathological and experimental studies of this disease in the East Indies in the opening decade of the present century were, as we can now see if we know the literature, well conceived and rightly directed, but those engaged did not have the advantage of the biochemical knowledge that the second decade was to provide. The biochemists, when they took over the study of the deficiency diseases, were similarly handicapped by a complete ignorance of the clinical and pathological features of beri-beri as a human disease.

They misconceived these and produced an ætiological theory not compatible with the facts of the disease and ignoring some of the most significant of them, such, for example, as its cardiac manifestations.

It required several further years of research by Rudolph Peters to begin to identify and to reconcile the biochemical lesion with the clinical and pathological facts, and even now this has not been completely achieved.

This kind of situation must repeat itself until there are sufficient amongst us who are both medically trained and also fit to go into the laboratory and work beside non-medical scientists, both parties knowing what they are about, and neither, through ignorance, at the mercy of the other.

It is encouraging to see the increasing recognition of this necessity in medical research. The most complex chemical and metabolic studies are now successfully carried on by physicians who handle the diagnosis, care and treatment of their own patients. Nor is metabolic medicine alone in this enterprising and far-seeing approach to clinical science.

In neurological medicine and pathology, which have always had a close attachment to scientific methods of investigation, we have, I feel, been too long and too exclusively preoccupied with the normal and disturbed activities of the neuron, and have neglected the study of the neuroglia in health and disease, though disorders of this element in the nervous system can wreck neural function as disastrously as can primary disease of the neuron. This is largely because experimental methods adopted in neuronal study are wholly different from those needed for the study of the neuroglia, and we have been too slow in widening our outlook on research. The example of disseminated sclerosis is one painfully familiar to us all, revealing as it does the crying need for a reappraisal of our research methods and outlook.

Training for Research

If there be any substance and importance in the plea which I am making for a wider research activity amongst both academic and part-time teaching-hospital physicians, the question which arises concerns what is being done or planned to give the necessary supplementary training to the young men and women who are to be the teachers and the research workers in the medicine of the future.

I suggest that our academic and professional bodies and organizations are not doing anything, and that in the recently founded fellowships so presciently set up by the Medical Research Council for graduates who are to return to clinical medicine we see the first recognition of the necessity for concerted action in this matter.

All our students pass through the statutory curriculum and the subsequent year of house appointments, and then in the middle 20s we make it necessary for the ambitious and aspiring to spend yet more time in acquiring a purely vocational higher qualification, namely the MRCP

Yet in essence the diploma is not a matter of further scientific training, but is primarily an endorsement of a status it is necessary to achieve before the young graduate is allowed to enter the ring and be viewed as a possible candidate for a place on the consultant staff of a teaching, or indeed of any hospital. In an increasingly hier-

archical profession, everyone must jump this Beecher's Brook, no matter what his future work is to be.

This traditional ritual is peculiar to us amongst the English-speaking countries. It does nothing to advance scientific medicine.

After this final ordeal by examination, conducted on lines that have not changed since the nineteenth century, the graduate, now nearer his thirtieth birthday, is no nearer being trained to undertake experimental studies in medicine than he was before.

Is it reasonable now to expect him to do what is necessary to acquire competence in some scientific discipline to fit him to undertake them? After all, the fulfilment of his ambition to attain consultant status on the staff of a teaching hospital may often depend on quite other considerations than his fitness to add to knowledge by these means.

With the prospect of economic security growing nearer to him, can we expect of him the heroic virtue of submitting himself to further training outside the clinical ring fence, where he is likely to be forgotten by those upon whom his opportunities depend?

I need not elaborate this theme, but in the circumstances it is not surprising that we are not turning out enough adequately trained clinical scientists. We have taken no reasoned measures to do so, and if in other fields of science the same haphazard attitude towards the higher education were the rule, we should have few scientists of the first rank.

Over twenty years ago, Thomas Lewis suggested means by which we might provide a foundation for this higher training for clinical science.

His idea was that the interested and promising student should, before he passes to the final and clinical stage of his medical education, be given or encouraged to take, a year's extra study of a science basic to medicine, such as physiology or biochemistry. Having achieved this he would return to the stream and complete his clinical training.

Such courses have long been available: at Oxford in the Final Honours School, at Cambridge in the second part of the Tripos, and in London in the Honours BSc course, which is perhaps, dare I say it, the most exacting of the three.

The student thus gains not only a fuller introduction to scientific method and thought, but also a year in mental and emotional maturity, and is at a great advantage if, subsequently, he feels moved to engage in research within the field of medicine.

It would be an interesting experiment, but one I do not expect to live to see, if one medical school were to decide to accept, for its final clinical course, no student who had not taken such a course.

Many interests would resist such a plan, many men would regard it as not likely to achieve its desired end since winners cannot always be picked in time, and probably the paralyzing combination of apathy, timidity, conservatism and indecisiveness would stifle such a project at its moment of conception. Certainly, there was no response to Lewis's simple suggestion, and a response to my more drastic remedy is even less probable.

It would require a band of real enthusiasts and idealists to achieve it, amongst whom a large quota of younger men would be essential.

Francis Bacon has said that young men are fitted for execution, old men for counsel. Certainly the first half of this aphorism is true, but I have never been persuaded that the second half is a reliable generalization. Thus, unless young men are interested in planning for the future, no such long-sighted planning as I have in mind is likely, for they must provide the impetus.

It was such a body of idealists, many of them young, that a few years ago gave birth to the College of General Practitioners, and no one can doubt what a powerful stimulus to higher standards of training and achievement in this branch of medicine this academically-minded body has already become.

Do no such fires burn in the young teaching hospital physicians of to-day?

I venture to submit, therefore, that unless we take systematic measures to train a proportion of medical students to be the clinical scientists of the future, we must fall behind those countries that have given thought to this problem. Whoever has travelled and has seen in some medical schools and hospitals overseas, the eagerness of the students in the best schools and the facilities and encouragement they receive in this respect will know the thoughts that must be in my mind.

I would urge my hospital colleagues to read once more, and to ponder the more detailed and reasoned statement of this case in Thomas Lewis's Huxley Lecture on 'Clinical Science within the University', published in the *British Medical Journal* in March 1935. He makes what I believe to be an unanswerable case for the plan of giving an extra year's scientific grounding to capable and ambitious students before they enter the final clinical stage of their hospital training, and against regarding what we now call the 'higher qualifications' as symbols of, or as necessary to, such a training; to which, indeed, as I have said, they bear no relation, useful as they may be as evidence of a higher level of competence in dealing with routine clinical problems.

Opportunity

Having said all this, a question yet remains to be asked. Of what use to train clinical scientists for our teaching hospitals unless we also go on to provide them with opportunities in their own country, and perhaps also in those of the Commonwealth overseas, to serve medicine through science?

Plans to increase the total number of hospital consultant physicians and to resolve the senior registrar problem are necessary and important, but they have nothing to do with the issue I am now considering. They simply increase the number and improve the status of trained men available to meet the routine demands of a National Health Service. Medicine is changing all the time, and the upgrading of physicians to consultant status is, of itself, not a contribution to the training or placing of clinical scientists. It is but a belated administrative device. Here I venture to remark in parenthesis that in what is becoming a status-obsessed profession, improving status is not to be confused with raising standards, which is quite another kettle of fish. Whatever the experience and ability of the physicians we upgrade, very many of them will work in small centres, or 'regions', which is the word I believe I should use, far removed from facilities for any kind of original work, and lucky in some instances if they have near at hand even the technical provision for all the diagnostic procedures now a part of practical medicine.

The existence of the problem I am now considering is not something we can reasonably expect to be noted by the lay administration of a National Health Service. One has to be inside the profession of medicine to understand its long-term needs, and even inside it, foresight is always a commodity in short supply.

When I hear discussion arising from the familiar question, 'what is the future of medicine?' I feel inclined to reply that for us, the pregnant question is, 'where is the future of medicine?'; that is, in what countries?

I have given voice this afternoon to some chastening thoughts. Of course, I do not expect them all to be received with enthusiastic approval. I have done this of set purpose, for to have given this lecture on a medical theme with which everyone could whole-heartedly agree would have been pointless, for it could have been no more than a sequence of glimpses of the obvious, and to offer this would not have been a compliment to this audience.

Therefore, I must leave you with my chastening thoughts, to accept, to select or to reject as you will, and thank you for the patience with which you have listened to me.

Section of Pædiatrics

President B E Schlesinger OBE FRCP

Meeting January 27 1961

Papers

Sporadic Goitre and Cretinism Due to the Production of an Abnormal Thyroid Protein

by James H Hutchison OBE MD FRCP (*Glasgow*)

Sporadic goitre and goitrous cretinism have been intensively studied in recent years in the United States, Holland, France and the United Kingdom. The use of radioiodine (^{131}I) has made it possible to elucidate many new facts about the pathogenesis of these intriguing and not very rare cases. Some of this research has been carried out in Glasgow by the author in close collaboration with Dr E M McGirr of the Muirhead Department of Medicine, Glasgow Royal Infirmary. Those facts which are reasonably well understood at present are:

(1) These cases are genetically determined, and the various groups fall into the ever-increasing list of inborn errors of metabolism. The mode of inheritance seems usually recessive (Hutchison & McGirr 1956).

(2) The enzyme deficiencies which cause them may vary in severity from case to case, even within the same family. When the deficiency is complete the result is goitrous cretinism; when it is partial, goitre develops without hypothyroidism.

(3) The effect on thyroid pathology is the same irrespective of which enzyme activity is missing. Deficient production of thyroid hormone results in increased pituitary thyrotrophic activity, and this leads to intense thyroid hyperplasia. In one case histological evidence of carcinoma has been found in the hyperplastic gland (McGirr, Clement, Currie & Kennedy 1959).

(4) At the present time, four clearly defined enzyme defects have been recognized:

(*a*) *Failure of the thyroid trap or pump:* The normal thyroid gland traps iodide from the blood stream to maintain a concentration which is twenty to thirty times that of the serum. The salivary glands and gastric mucosa have a similar ability. Last year, Stanbury & Chapman (1960) from Boston described the first case in which this trapping mechanism, not only in the thyroid gland but also in the salivary glands and gastric mucosa, had failed. The evidence was a very low uptake of ^{131}I after a tracer dose; the inability of tissue slices from a thyroid biopsy to concentrate iodide or to make an appreciable amount of protein-bound iodide; and a remarkably small amount of iodine in the patient's gland.

(*b*) *Failure of organic binding of iodide:* After the thyroid gland has trapped iodide it is rapidly oxidized to elemental iodine by a peroxidase. This step is essential for the incorporation of iodine into a protein-bound complex in combination with tyrosine. When peroxidase activity is absent the thyroid gland traps iodide with excessive avidity but, as the iodide cannot be combined with protein, the administration of anions such as thiocyanate and perchlorate will cause its abrupt and immediate discharge from the gland. This test is easily performed after a tracer dose of ^{131}I. Stanbury & Hedge reported the first cases of this type in 1950. Their frequent, if not constant, association with congenital deafness was subsequently noted in this country by Morgans & Trotter (1958) and by McGirr and myself (McGirr, Hutchison & Clement 1959*a*).

(*c*) *Failure of coupling of the iodotyrosines:* In the normal gland triiodothyronine is formed by the coupling of one molecule of monoiodotyrosine with one molecule of diiodotyrosine, and thyroxine by the coupling of two molecules of diiodotyrosine. If the coupling enzyme were to be absent the result would be a hyperplastic gland which was full of the iodotyrosines but which contained little or no hormone. This defect is less well established as its demonstration requires a thyroidectomy after a large dose of ^{131}I. Furthermore, the evidence in favour of absence of a coupling enzyme is indirect and only inferential. The first case was described in 1955 by Stanbury *et al.* It seems to be rare, and McGirr and I have

seen only one case in which we were reasonably satisfied that this was the true explanation.

(*d*) *Failure of dehalogenation of the iodotyrosines:* In the normal gland the iodotyrosines and iodothyronines are stored in the thyroglobulin. When the target cells require more hormone, thyroglobulin is digested by thyroid protease. The iodothyronines thus liberated cross the cells to enter the blood, but the iodotyrosines set free at the same time do not. This is because they are deiodinated by dehalogenase and their iodine is conserved for further hormone synthesis. If dehalogenase activity is missing there is a constant drain of iodotyrosines from the gland to the blood and thence to the urine. This appears to be one of the commonest of the thyroid inborn errors, and we have detected 24 cases. The simplest diagnostic test is an oral dose of radioactive monoiodotyrosine (^{131}I). In normal individuals it is deiodinated so that it is excreted in the urine in the form of iodide. If there is a dehalogenase deficiency it mostly appears in the urine unchanged. Slices of thyroid tissue from such cases also fail to deiodinate labelled monoiodotyrosine *in vitro* in contrast to normal thyroid tissue (Querido *et al.* 1956, McGirr, Hutchison & Clement 1959*b*).

All who have worked in this field, however, have encountered cases in which radioiodine studies yielded results which were incompatible with any of these 4 enzyme deficiencies. It has been obvious that there are other intrathyroid defects yet to be defined. From such a miscellaneous group, we have isolated 6 goitrous patients in whom our tests yielded results so similar as to suggest that they shared a common pathogenesis, the production of an abnormal iodinated thyroprotein which spilled over into the blood. Three of these were sisters with enormous goitres, although only 1 was hypothyroid at the time of examination; 2 were cretinous brothers with small goitres; the sixth case was a mildly hypothyroid boy with a moderate goitre.

Gland Uptake and Serum ^{131}I Studies

In all of these patients the thyroid gland took up a dose of ^{131}I with excessive speed and in excessive amounts. Potassium perchlorate failed to cause any discharge of iodide from the gland, thus excluding a deficiency of peroxidase. Dehalogenase activity was also shown to be normal. In 4 patients a dose of radioactive monoiodotyrosine was normally deiodinated; in one, slices of thyroid tissue deiodinated monoiodotyrosine *in vitro*. The important common denominator in all 6 cases was found in the serum levels of ^{131}I estimated forty-eight hours after a tracer dose. The serum protein-bound ^{131}I was misleadingly high and, in fact, in the thyrotoxic range. On the other hand, there was an apparent discrepancy in that only a small proportion of the protein-bound ^{131}iodine was extractable by butanol, which extracts thyroxine and iodotyrosines from the serum. These findings, repeated in all 6 cases, led us to believe that some abnormal iodinated compound, which was not butanol-extractable, was included with the protein-bound iodide.

We made further tests on the serum of 2 of our patients. We found that the butanol-extractable fraction could not be increased by digestion with trypsin, but that it rose substantially after digestion with chymotrypsin. Furthermore, butanol extraction followed by treatment of the extract with 5% sodium carbonate in 4N sodium hydroxide (Taurog & Chaikoff 1948) revealed that this abnormal iodoprotein contained both thyroxine-like and iodotyrosine-like compounds. It seemed, therefore, that although these patients were hypothyroid and although they had normal thyroid dehalogenase activity, both thyroxine and the iodotyrosines were, in fact, present in their serum. These compounds were, however, apparently contained within an abnormal serum protein.

Little is known as to how the protein-bound thyroid hormones in the blood of normal subjects are detached to reach their target. We presume the process is enzymatically controlled. I suggest that in our 6 patients some of the thyroid hormones are liberated from the gland abnormally bound to protein or bound to an abnormal protein. If this were so an extrathyroid enzyme might fail to act upon such an abnormal substrate. Similarly, if the iodotyrosines were incorporated in an abnormal thyroprotein, or if there was an abnormal proteolytic digestion of normal thyroglobulin, intrathyroid dehalogenase might fail to deiodinate them so permitting the escape of iodotyrosines into the blood.

A similar, but possibly not identical, abnormal iodoprotein has been found in the sera of patients with thyroid carcinoma (Robbins *et al.* 1955; Tata *et al.* 1956) and in 2 patients with goitrous hypothyroidism (Di George & Paschkis 1957; De Groot *et al.* 1958).

Chromatographic Studies of Thyroid Tissue

In one case we were able to study the radioiodinated compounds within the thyroid gland after thyroidectomy which was performed forty-eight hours after 1 mc of ^{131}I.

Portions of the thyroid tissue were homogenized and digested by trypsin and chymotrypsin in barbitone buffer at pH 8·6. Ascending chromatograms were then run in various solvents – butanol acetic acid, butanol ammonia and amyl alcohol ammonia. After drying and staining of the markers the chromatograph strips were scanned for radioactivity by passing them between two Geiger-

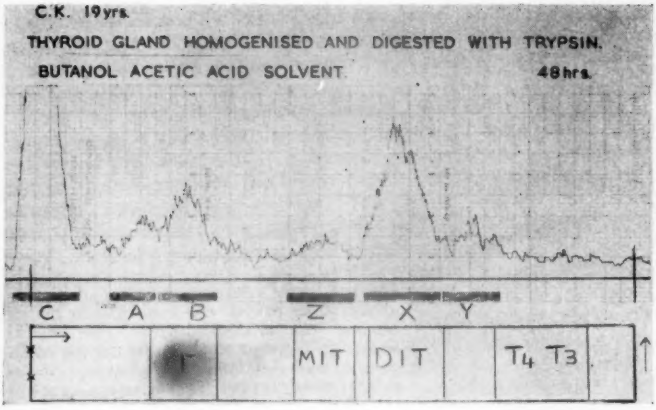

Fig 1 *Scan for radioactivity of ascending butanol acetic acid chromatogram of trypsin digest of thyroid gland. Three unidentified zones of radioactivity (C, A and Y). Iodide, monoiodotyrosine and diiodotyrosine (zones B, Z and X) present. No identifiable triiodothyronine or thyroxine. (Figs 1–4 are reproduced by courtesy of the* Scottish Medical Journal).

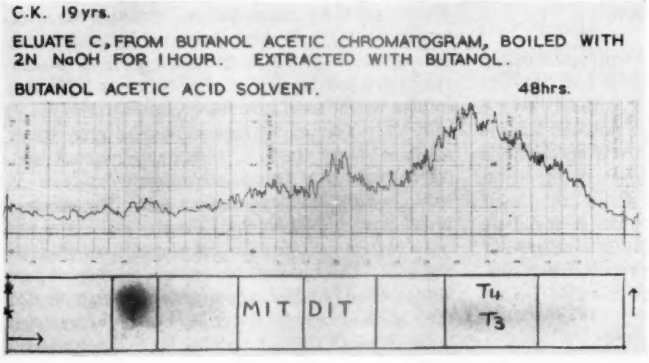

Fig 2 *Scan of ascending butanol acetic acid chromatogram of zone C (Fig. 1) after boiling for one hour in 2N NaOH and acidification. Triiodothyronine and thyroxine have been liberated as well as some mono- and di-iodotyrosine*

Müller counters connected through a rate-meter to a recording milliammeter.

A scan of a butanol acetic acid chromatogram of a trypsin digest of thyroid gland is shown in Fig 1. Iodide (zone B), monoiodotyrosine (zone Z) and diiodotyrosine (zone X) were clearly identified. The low ratio of monoiodotyrosine to diiodotyrosine, which is abnormally low, contrasts with the abnormally high ratios found in the other types of goitre which we have studied. No thyroxine or triiodothyronine appeared after trypsin or chymotrypsin digestion. There were, however, 3 unidentified zones of radioactivity (Y, A, C). We have met with 'Y' in other types of thyroid gland and its significance is not known. Elution studies have shown that it is not diiodothyronine (McGirr *et al.* 1960). Zone A was shown by elution studies to come, at least in part, from zone B which was iodide. The zone of real interest is 'C' which comprised the major part of the radioactivity in all the chromatograms. At first it was thought to be normal thyroglobulin which had remained undigested. It resembled thyroglobulin in being non-extractable by butanol. However, unlike thyroglobulin it proved resistant to redigestion with trypsin when the origin of the chromatogram was placed in barbitone buffer at pH 8·6. But, when it was boiled with 2N sodium hydroxide for one hour and then acidified, 80% of its radioactivity became butanol extractable. Chromatograms of the butanol extract run in butanol acetic acid (Fig 2) and other solvents

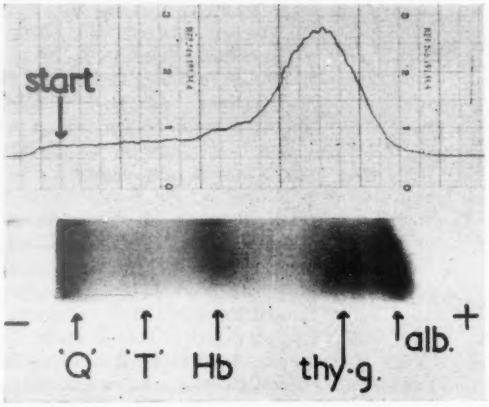

Fig 3 *Scan of electrophoretogram of thyroid extract from case of non-toxic nodular goitre. Stained with bromphenol blue. Five protein bands: Q, T (gammaglobulin), Hb (hæmoglobin), thy-g. (thyroglobulin), alb. (albumin). Radioactivity mainly in thyroglobulin zone.*

showed that zone C had broken down mainly to thyroxine, although some mono- and di-iodotyrosine were also present. The only thyroxine in the gland appeared to be in this iodine-containing compound which remained at the origin of the chromatogram of the trypsin digest.

It is tempting to assume some relationship between this abnormal compound and the abnormal iodoprotein which was present in the serum of our patients. Both were non-extractable by butanol. They were not identical because the serum compound was broken down by digestion with chymotrypsin whereas the gland compound resisted digestion by chymotrypsin. It could be that the serum compound yielded to the action of chymotrypsin because it had previously been subjected to the action of thyroid protease before leaving the thyroid substance.

Electrophoretic Studies of Thyroid Tissue

Finally, we examined extracts of the thyroid tissue by electrophoresis, using a technique described in detail elsewhere (Watson *et al.* 1960). Our experience with this method is too limited to justify any dogmatism but the results were interesting. In Fig 3 is shown an electrophoretogram of normal thyroid tissue extract. Five protein bands are present. 'Q' is of uncertain significance but we have found it in most glands examined. It may be a normal thyroprotein or it may be an artifact of our method. Certainly it is not normally iodinated. The main radioactivity is in the thyroglobulin and albumin zones. The electrophoretogram (Fig 4) from the thyroid extract of our patient showed a very different picture. Stainable thyroglobulin was not visible. There was a broad band of radioactivity which extended through and beyond the zones normally occupied

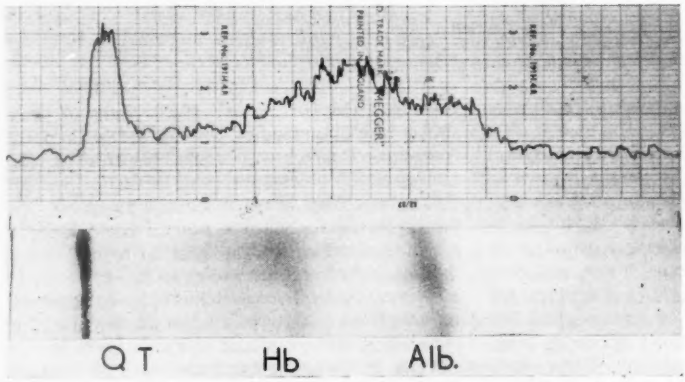

Fig 4 *Scan of electrophoretogram of thyroid extract from case of familial goitre. Thyroidectomy performed forty-eight hours after 1 mc ^{131}I. Four protein bands: Q, T, Hb and alb. Radioactivity extends through and beyond thyroglobulin and albumin zones. Q zone is also apparently iodinated*

by thyroglobulin and albumin. There was also a marked peak of radioactivity corresponding to the Q band and indicating that this thyroprotein was, in fact, iodinated.

These are obviously significant findings. We cannot supply a wholly satisfactory explanation, but we are probably justified in our conclusion that in these 6 patients there was formed an abnormal iodinated thyroprotein. This compound, or a derivative of it, spilled over into the blood but the thyroxine contained within was apparently not released to the tissues. The goitres were presumably due to a compensatory over-activity of pituitary thyrotrophin. The relative adequacy of this compensatory effort, in relation to the demands of growth, would determine whether or not the individual patient stayed euthyroid or became hypothyroid.

The familial incidence indicates that this type of goitre is also a genetically determined inborn error of metabolism.

Summary

(1) Four types of inborn error of intrathyroid metabolism which cause sporadic goitre with or without hypothyroidism are at present reasonably well defined.

(2) A fifth is described in 6 patients in whom there was evidence of the production of an abnormal thyroid protein. This compound or a breakdown product could also be demonstrated in the serum. Although it contained thyroid hormone as well as iodotyrosines four of the 6 patients were hypothyroid.

(3) The goitres were presumed to be due to compensatory over-activity of pituitary thyrotrophin production.

(4) The familial incidence indicates that this is yet another genetically determined intrathyroid deficiency.

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Hæmolytic Mechanisms in some Hereditary Anæmias

by T A J Prankerd MD MRCP (*London*)

Cross-transfusion experiments have demonstrated a basic pathological principle underlying the pathogenesis of hæmolytic anæmias. This has made it possible to relate the pathogenesis either to an abnormality of the cell or of its environment. The hæmolytic anæmias which have a hereditary background are all characterized by a cellular abnormality and their hereditary nature suggests that we must look at the physical and chemical structure of the red cell for an explanation of its inability to survive normally in the circulation.

There are four obvious attributes of the red cell which theoretically may be involved in cellular defects: (1) Cell shape, (2) cell membrane, (3) cell metabolism, (4) hæmoglobin molecule. Their relevance to the hæmolytic process in this group of anæmias will be considered.

(1) *Cell Shape*

Although the normal red cell is capable of reversible transformation to any form between the normal biconcave disc and a sphere of the same surface area it is most likely that the deformed shape of abnormal red cells, which is irreversible, is a consequence of some change in chemical structure, involving the membrane or the hæmoglobin molecule, or a change in metabolism. However, knowledge of the relationships between shape and structure is still slight and it is useful to consider shape changes as separate entities although they presumably must have a molecular cause. Two predominant abnormalities of shape are found in hæmolytic diseases with a number of less common ones.

Leptocytes, which are flat red cells with increased osmotic resistance, often have an increased diameter. The extreme form is the target cell. Such cells usually have a shortened life span if transfused into normal subjects, but an exception to this generalization are the thin cells of iron deficiency anæmia which have a normal survival (Table 1). These cells do not have an increased diameter and this may be the important factor underlying the difference in cell survival. Target cells are commonly seen in thalassæmia and the hæmoglobinopathies, and those hæmolytic states associated with abnormal hæmoglobins always show target cells in their circulation.

Spherocytes are cells with decreased osmotic resistance and they invariably have a shortened survival. These cells are a characteristic of hereditary spherocytosis, but in this disease it is probably not the cell shape which is the primary cause

Table 1
^{51}Cr survival of tagged target cells in normal recipients

	$T\frac{1}{2}$ ^{51}Cr *days*
Normal	25–29
Obstructive jaundice	12
Thalassæmia 1	10
2	16
3	18
Hæmoglobinopathies C	18
H	20
SC	10 (unsickled)
Iron deficiency	24
	26

of hæmolysis. Two experiments demonstrate this very well. Firstly, Crosby & Conrad (1960) have induced a state of iron deficiency in patients with hereditary spherocytosis by repeated bleedings, and have found that even when the cells have become flat and are no longer spherical the rate of hæmolysis of labelled cells is unchanged. Secondly, we have found (Prankerd 1960) from studying red cell survival in members of one family, some of whom showed marked and others only slight spherocytosis, that the degree of spherocytosis did not influence cell survival. It is common clinical knowledge that splenectomy cures the hæmolysis in this disease, and the well-known observation that spherocytes of any nature are trapped in the spleen at first sight seems difficult to reconcile with the conclusion that hæmolysis is not directly related to the degree of red cell sphering. Some work which will be discussed below suggests that the spleen conditions hereditary spherocytic cells in some way during their circulation and that it is only after a period of conditioning, which may produce physical and metabolic changes, that cell destruction occurs.

Sickling is another common morphological change in red cells which is associated with hæmolysis, and in this case the mechanism of lysis appears more obvious. Deoxygenation of sickle hæmoglobin results in the formation of tactoids, or partly crystalline structures, in the hæmoglobin solution; such structures forming in red cells are probably responsible for the bizarre shape changes which render the cell more rigid. These phenomena lead to changes in blood viscosity and capillary blood flow as well as cellular changes which include increased mechanical fragility, metabolic changes and increased autohæmolysis (Griggs & Harris 1956, Prankerd 1955) any of which could seem to be responsible for intravascular lysis.

Other morphological abnormalities are found in some hereditary hæmolytic diseases such as ovalocytes and acanthrocytes, but less is known about these conditions. In the case of ovalocytosis it does not appear that the cell shape is contributory to hæmolysis since hæmolysis is only variably associated with the morphological abnormality, cell metabolism is normal and we know nothing about the hæmolytic mechanism (Dacie 1960).

(2) *Cell Membrane*

The membrane of the red cell has received scant attention, probably because methods of lipid analysis have been slow in development. Removal of red cell lipid, as by washing, reduces cell survival so that lipid defects in the membrane could reasonably be a chemical basis for hæmolysis in these diseases. Examples of possible lipid defects are the red cells of thalassæmic patients which appear to contain a deficiency of cerebroside, and an abnormality of cell phospholipids which has recently been reported in hereditary spherocytosis (Allison *et al.* 1960). It is possible also that acanthrocytes are cells with abnormal lipid constituents.

Unfortunately the protein of the red cell membrane does not seem to have been subjected to much pathological investigation. This is probably because it is so insoluble and fibrous in nature that manipulation becomes technically difficult.

(3) *Metabolism*

The red cell depends on the anaerobic breakdown of glucose for its supply of energy which is stored in the form of adenosine triphosphate. Energy is released from this compound and probably helps to maintain the osmotic balance, membrane structure and the shape of the cell.

A number of defects in glucose metabolism have been recorded in red cells of patients with hereditary hæmolytic anæmia (Prankerd 1961). In hereditary spherocytosis intracellular metabolism is imperfect although overall glucose utilization is normal. A defect can be revealed by labelling intracellular phosphate esters with ^{32}P when there appears to be a reduction in the rate of phosphorylation of various esters. Instability of these phosphate esters can also be revealed by incubating the cells in the absence of glucose, a phenomenon which is probably the basis of the increased autohæmolysis of this disease. What role the metabolic defect of these cells plays in producing the hæmolysis of the disease is not clear but some experiments with artificial spherocytes suggest it may be important.

In congenital nonspherocytic hæmolytic anæmias defects in cell metabolism have also been reported; some of these are gross and involve almost complete cessation of glycolysis, in other instances diminished adenosine triphosphate, or increased concentrations of 2, 3-diphosphoglycerate have been reported. In one family under the care of Dr Bernard Schlesinger, studied by me there were low levels, and rates of labelling, of 2, 3-diphosphoglycerate which appeared to be

the result of a deficiency of the enzyme diphosphoglyceromutase. Apart from glucose 6-phosphate dehydrogenase deficiency this appears to be the only specific enzyme defect yet found in these hæmolytic anæmias.

Glucose 6-phosphate dehydrogenase deficiency is not common in this country in spite of our present large immigrant population. Out of some hundred tests in suspected subjects we have only detected two instances. The defect, which is inherited as a sex-linked incompletely dominant character, usually gives rise to susceptibility to hæmolysis in homozygous individuals after the administration of a number of different agents. The following may be involved (Beutler 1959):

Acetanilid	*Vicia fava* bean
Acetophenetidin	Naphthalene
Amidopyrine	Nitrofurantoin
8-amino quinolines	Para-aminosalicylates
(Primaquine)	Phenylhydrazine
(Pamaquin)	Sulphanilamide
Amino-salicyl-sulphonamides	Vitamin K (synthetic derivates)
Antipyrine	

Because of a decrease of the concentration of this enzyme in the cell as it ages, only cells of a certain age are susceptible to lysis, and the hæmolytic process is therefore self-limiting. In between exposure to the agents mentioned, enzyme-deficient individuals show no evidence of hæmolysis. However, another group of patients with a similar enzyme defect have been described who show continuous hæmolysis dating from birth or early infancy and who have been regarded as examples of congenital nonspherocytic hæmolytic anæmia (Rothberg *et al.* 1959). We have not yet observed any patients such as these.

Glucose 6-phosphate dehydrogenase deficiency results in a failure of the normal metabolic processes in the red cell which maintain the stability of hæmoglobin. In the presence of any of the various agents mentioned hæmoglobin undergoes an oxidative denaturation with the formation of a number of intermediates, amongst which are the familiar Heinz bodies which are seen in the cells of affected individuals during hæmolytic episodes. After cross-transfusion of cells containing Heinz bodies such cells are rapidly removed from the circulation and destroyed predominantly in the spleen (Shahadi *et al.* 1959). Another substance, glutathione, is also almost certainly involved in the processes maintaining hæmoglobin in its natural state, and the ready oxidation of reduced glutathione in enzyme-defective cells was the first observation of any chemical abnormality in the red cells in this disorder, and has been used as a means of detection of enzyme deficient individuals.

(4) *Hæmoglobinopathies*

Apart from the sickling process, which leads to red cell destruction perhaps by both mechanical and metabolic means, the pathogenesis of the hæmolysis which may occur in certain other hæmoglobinopathies is still obscure. However, the occurrence of target cells in these hæmolytic states is invariable and it is possible that this morphological, and perhaps chemical, abnormality is a principal factor in shortening red cell survival.

Role of the Spleen

Last of all one must consider the role of the spleen in the hæmolytic processes of these diseases. It is obviously of principal significance in those anæmias which can be cured by splenectomy and, of those discussed, hereditary spherocytosis alone benefits invariably from this procedure. Splenectomy in hereditary spherocytosis appears to be beneficial partly because spherocytic cells are principally sequestered in the spleen, a phenomenon which can be detected by surface counting after the injection of radioactively labelled red cells (Jandl *et al.* 1956).

Experiments indicate that spherocytes with normal metabolism can withstand a period of splenic trapping whereas those in which metabolism is defective cannot (Prankerd 1960). Furthermore, cells which have been trapped in the spleen undergo osmotic and probably metabolic conditioning in the circulation as a result of repeated passage through the spleen (Motulsky *et al.* 1958). This has been shown by cross-transfusion experiments of blood from two hereditary spherocytic patients, one of whom had had a splenectomy, and from a study of red cells taken from different sites of splenic circulation.

In other conditions such as sickle-cell anæmia and some congenital non-spherocytic forms, splenic trapping can be demonstrated with the aid of isotopically labelled red cells, but it is not exclusive to the spleen and trapping in other sites such as liver and bone-marrow also occurs. Splenectomy in these instances is clearly not going to be particularly beneficial.

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The Tryptophan Load Test in the Syndrome of Infantile Spasms with Oligophrenia

by B D Bower MD MRCP DCH (*Birmingham*)

Pædiatricians are familiar with the rare and tragic type of infantile epilepsy variously known as infantile spasms, lightning fits, salaam spasms or Blitz-Nick-und-Salaam-krämpfe. The tragedy lies in the fact that the malady often strikes an apparently normal infant and causes severe mental regression which is usually permanent even though the epilepsy may finally die out. We are ignorant of the nature of the cerebral insult in infants with such a history (the cryptogenic group), although in some cases immunizing procedures are suspect. An approximately equal number of infants develop these characteristic fits as a consequence of recognizable cerebral disease or damage, which is usually prenatal or perinatal; but the blow is less devastating in this group (the symptomatic group), as these children have been mentally retarded from birth and we have a reason for their epilepsy and mental handicap.

Gastaut (1960) has divided the history of the study of infantile spasms into three periods. The first, the clinical period, was concerned with delineating the clinical features and natural history. Then in 1952 he (Gastaut & Rémond 1952) and Gibbs & Gibbs (1952) in the U.S.A., described the chaotic epileptic EEG pattern called by the latter 'hypsarrhythmia'; this was the start of the second or EEG period. I wish to emphasize that hypsarrhythmia is a descriptive term for an EEG pattern, not a disease, and the terms 'infantile spasms' and 'hypsarrhythmia' are not synonymous. The two characteristics of hypsarrhythmia are chaos and high amplitude and a truly hypsarrhythmic record is, in our experience, found in only a little more than half the first records of cases of infantile spasms (Bower & Jeavons 1959). The remaining cases have an epileptic but not a hypsarrhythmic record. A normal EEG is therefore very much against the diagnosis. A hypsarrhythmic record is almost diagnostic but it is not uncommon to find a less specific epileptic record.

The third period, the period of hormone treatment, started in 1958 with Sorel's discovery that corticotrophin can stop the spasms and produce a normal EEG pattern (Sorel & Dusaucy-Bauloye 1958). This has been confirmed by many, and now in 1961 it is possible to assess the results of treatment with this and other hormones more precisely, although not yet as clearly as one would like. As these results are relevant to what follows, our findings at the Children's Hospital, Birmingham, are briefly described.

We have treated 33 children. Of these 19 are classified as cryptogenic and 14 as symptomatic. Most of the symptomatic group are children with clear evidence of cerebral birth injury. Corticotrophin, prednisolone or dexamethasone was used. A course lasted at least a month, and dosage was at or above the accepted levels for full therapeutic effect in other diseases. There was little difference between the immediate results of each drug and they will not be considered separately. In 31 of the 33 patients the EEG improved on treatment and the spasms became fewer; in 27 spasms stopped altogether. Fig 1 shows a good result. EEGs were taken twice weekly and each record was given a score according to a system devised by my colleague, Dr Peter Jeavons (Jeavons & Bower 1961). Points are given for various abnormal features; hypsarrhythmia scores high (over 12) and more organized epileptic records score lower, while a normal record or one showing a non-specific abnormality scores 0 or 1. After the start of corticotrophin therapy there was a steady fall in score and a cessation of spasms, and in this case the improvement has been maintained for eighteen months. In two-thirds of our cases, however, there has been a relapse after treatment was stopped, and this was most marked in the symptomatic group. The most disappointing feature of treatment is the failure of mental improvement over the period of follow-up in spite of an initial promise during treatment. We have used Griffiths' testing (1954) before and on several occasions after treatment, and in only 3 of the 23 who have been followed longest has there been a significant improvement (Bower & Jeavons 1961). This result is no better than that in our untreated series (Jeavons & Bower 1961).

This very definite effect of corticotrophin and adrenal steroids upon the epilepsy and upon the EEG, even though temporary in many instances, was surprising in 1957 and is still unexplained. It is something more fundamental than the effect of the anticonvulsants, for such an improvement in the EEG appearance is never produced by anticonvulsants, which are clinically ineffective in this condition. It is not due to correction of hypoglycæmia, for this is never present. Nor is there any evidence of any major water-and-salt imbalance (although at the cellular level this would be difficult to detect), and this seems unlikely; dexamethasone, a corticoid with a minimal effect on water-and-salt balance, seems as effective as corticotrophin. An anti-allergic or anti-inflammatory action is also an unsatisfactory explanation, since there is a very definite improvement in some of the symptomatic cases, in whom the brain

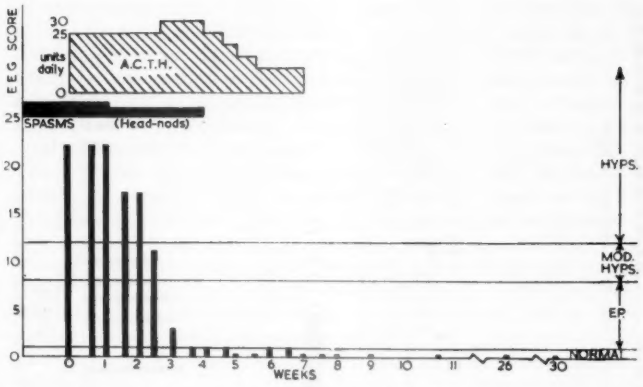

Fig 1 *Improvement of spasms and EEG on corticotrophin*

damage was caused by mechanical or anoxic factors operating several months before the drug was given. A more attractive hypothesis is that adrenal steroids cause maturation of enzyme systems which raise the epileptic threshold, and which have been disturbed by the cerebral insult, whatever its nature. There is experimental evidence that steroids can cause increased enzyme activity in animals (Knox *et al.* 1956).

Cochrane (1959) found evidence of pyridoxine deficiency, that is an abnormal tryptophan load test, in five patients with the syndrome of infantile spasms and mental retardation; and he was satisfied that there was a clinical and EEG improvement after large doses of pyridoxine were given. This report stimulated us to apply the tryptophan load test to our patients before hormone treatment and during treatment to see if the beneficial action of corticotrophin and adrenal steroids could be explained by a corrective action on disturbed pyridoxine metabolism.

Pyridoxine, usually as pyridoxal phosphate, is needed as co-enzyme in an almost embarrassingly large number of cerebral metabolic processes, and it is not difficult to imagine severe disturbance of brain function when it is deficient. For instance, it is needed in the Krebs cycle and for making glucose available as a source of energy. Two metabolic processes seem particularly relevant to the syndrome under consideration. Pyridoxal phosphate is needed for the formation of serotonin (Fig 2), a substance which is probably very important in cerebral metabolism. It has a sedative action and animal experiment has suggested that it is a powerful inhibitor of synaptic transmission (Marrazzi & Hart 1955), so that deficient formation of serotonin might well lead to convulsions. Pyridoxal phosphate is also needed to form gamma-amino-butyric acid (GABA) in the brain from glutamic acid. A large amount of information has recently been acquired about GABA and its inhibitory properties on the C.N.S. It has an anticonvulsant action; by its administration artificially induced convulsions can be prevented in animals (Hawkins & Sarett 1957) and *grand mal* and *petit mal* fits have been prevented in human beings (Tower 1960).

From these data one is not surprised that pyridoxine-deficient animals develop fits, or that the infants who were given a pyridoxine-deficient dried milk in the United States in 1951 and 1952 developed fits which were immediately relieved

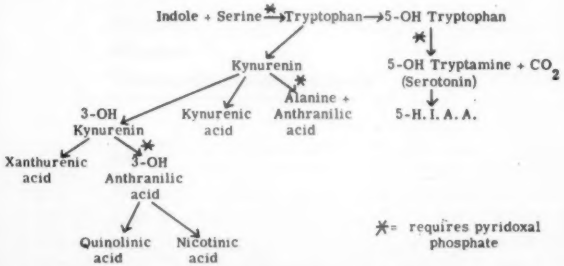

Fig 2 *Tryptophan metabolism* (after *Tower 1956*)

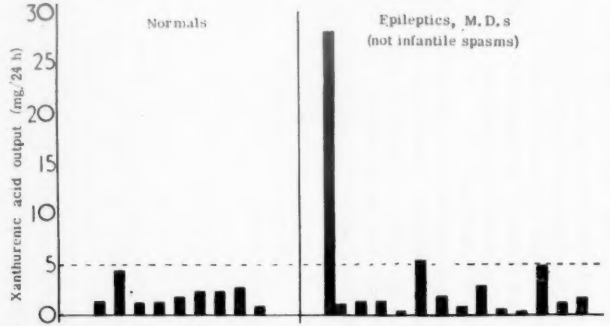

Fig 3 *Results of tryptophan load test – controls. The cross-hatched square shows the result after treatment (i.e. 2·1mg)*

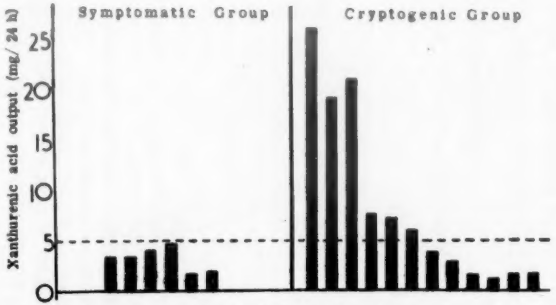

Fig 4 *Results of tryptophan load test – infantile spasms (before treatment)*

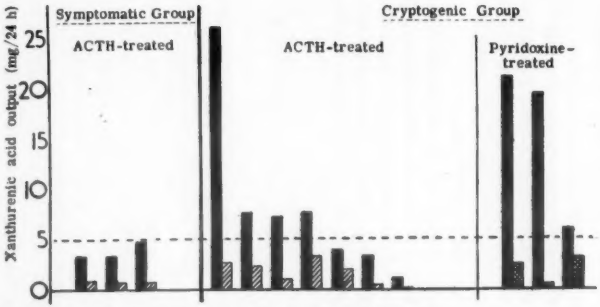

Fig 5 *Results of tryptophan load test – infantile spasms. Solid columns, before treatment. Hatched columns, during treatment. Cross-hatched columns, during treatment with pyridoxine*

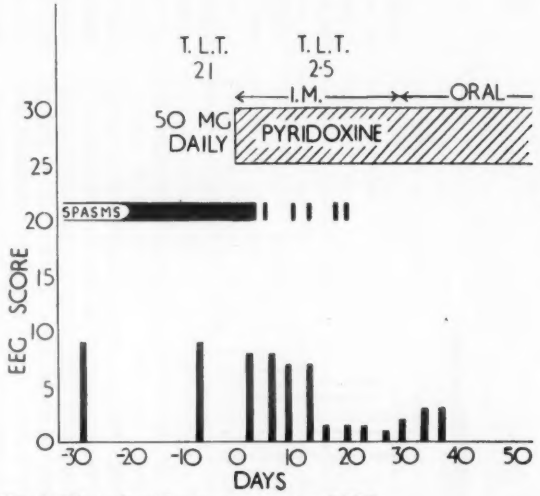

Fig 6 *Effect of pyridoxine on spasms and EEG*

by administration of pyridoxine (*see* May 1954). One of the methods of demonstrating pyridoxine deficiency is to use the tryptophan load test, and the theoretical basis for this test can be understood from Fig 2. Normally one of the paths of metabolism of tryptophan is through kynurenin, 3-OH kynurenin, 3-OH anthranilic acid and nicotinic acid. The third step requires pyridoxal phosphate as a co-enzyme and in pyridoxine deficiency this pathway is blocked. As a result, the alternative pathway is taken and xanthurenic acid is formed. Normally little or no xanthurenic acid is found in the urine, but under these circumstances it can be detected and measured, especially if the patient is given a load of tryptophan beforehand. The details of the test as we have carried it out are as follows:

(1) Collect urine for twelve hours before tryptophan administration. Estimate xanthurenic acid. Multiply by 2.

(2) Give dl-tryptophan: 0·4 g/kg body weight (0–3 years). 0·2 g/kg bodyweight (3 years upwards).

(3) Collect urine for twenty-four hours afterwards. Estimate xanthurenic acid.

(4) Subtract first result from second.

The dose of tryptophan is that which Cochrane (1960) used. Fig 3 shows the result of our attempt to establish a normal figure. Twenty-two children served as controls. On the left are the results in 9 children admitted to hospital for conditions unlikely to be associated with pyridoxine deficiency and with no evidence of disease of the nervous system and no convulsions. On the right are the results in 13 children in whom we had no reason to suspect pyridoxine deficiency but who had convulsions or mental deficiency or both. We excluded children with infantile spasms. The ages range from 2 months to 12 years. Only one result was obviously different from the others, and this child turned out to have pyridoxine deficiency or dependency. He was mentally normal but had had uncontrollable fits since 3 weeks of age. At 18 months the tryptophan load test gave this abnormal result and he was then treated with pyridoxine; his fits were completely controlled and his tryptophan load test result fell from 28·5 to 2·1 mg of xanthurenic acid/24 h. This gave us some confidence in the test. All the other results are below 5 mg/24 h and we felt that this figure should be taken as our normal.

Fig 4 shows the results obtained in 18 children with infantile spasms before corticotrophin or steroid were given. The 6 in the symptomatic group were within normal limits. Of the 12 cryptogenic cases, however, 6 were outside our normal limit of 5 mg; 3 are very definitely abnormal, and 3 are just outside our normal and their significance could be disputed. There is no obvious difference in the history, or in the severity of the epilepsy, the mental defect or EEG abnormality to account for the difference between the patients with an abnormal result and those with a normal one. A severe acute infection can produce an abnormal result but this was not the case here. Nor did their dietary history suggest any deficiency of pyridoxine intake. Our results therefore confirm Cochrane's view that there is some evidence of a disturbance of pyridoxine metabolism in this syndrome, but this applies to only half our cryptogenic cases.

The results of the tests carried out during ACTH or steroid treatment are more uniform. The test was done when there was a diminution or cessation of spasms and a definite EEG improvement: this was usually about two or three weeks after the start of treatment. Nine of the 18 patients whose results were shown in Fig 4 were given a second test during corticotrophin treatment and 1 was tested during dexamethasone treatment. The results of these 10 patients are shown in Fig 5. In every case there was a definite reduction in xanthurenic acid output, whether the pre-treatment result was outside the normal limit or not: in every case but one the treatment figure is less than half the pre-treatment one, and this applied to the symptomatic as well as to the cryptogenic cases. This reduction of xanthurenic acid output on treatment has been confirmed by chromatography of these specimens.

The next logical step was to do what Cochrane had done, use pyridoxine instead of corticotrophin or steroids, but there was an ethical problem here. It seemed most unlikely that these patients had simple pyridoxine deficiency and that a dramatic cure would result. We knew that steroids had a beneficial effect and when we were hopeful that the early use of steroids might improve the mental level, it seemed unjustifiable to withhold hormone treatment, so only 3 children have so far been given pyridoxine. Two were chosen as particularly suitable because they had very abnormal pre-treatment tests (2 of the 3 very abnormal ones in Fig 4) and they were not early cases. In order to get the greatest effect the daily dose of pyridoxine was very large (50 mg daily – the normal requirement is about 1 mg daily for infants) and it was given intramuscularly. All 3 showed improvement in their tryptophan load test during treatment, xanthurenic acid output becoming normal (Fig 5).

The first child showed an encouraging clinical response (Fig 6). Spasms stopped and the EEG improved, although not quite reaching normality. There was no dramatic mental improvement and his development quotient was unaltered, but there was a definite change in his behaviour. Whereas before treatment he had sat in his cot and spent

long periods making bizarre movements with his hands and face, after three weeks these movements stopped and he started to walk round his cot. Unfortunately this improvement was not maintained. He was given the same daily dose of pyridoxine orally and sent home. Two months later his bizarre tics and his infantile spasms started again and his EEG was worse. This time his tryptophan load test was normal. Intravenous pyridoxine produced no change in his EEG over the subsequent two hours and another two months' intramuscular pyridoxine had no effect. In the case of the second child with a very abnormal tryptophan load test, neither intravenous nor seventeen days' intramuscular treatment had the slightest clinical or EEG effect, although the tryptophan load test became normal. In the third child fits stopped and his EEG became normal but he was probably improving spontaneously as one of his previous EEGs had been normal.

More patients must be treated with pyridoxine in order to clarify the question of its usefulness in the infantile spasms syndrome. Already, however, we can say that this is not a matter of simple pyridoxine deficiency. In pyridoxine deficiency there is a rapid response to intravenous injection which is seen in the EEG record within a few minutes. We gave pharmacological doses but the response in the first case took two weeks to occur and during the second period of treatment there was no response. Nor did the second case show any benefit. Nevertheless a definite response occurred in the first case as it did in Cochrane's 5 cases. This fact, and the fact that the clinical and EEG response to hormone treatment was consistently accompanied by an improvement in the tryptophan load test, make one feel that pyridoxine is intimately concerned. Possibly steroids make pyridoxine available to the cell. It is interesting that Low *et al.* (1958) were able to improve a patient with infantile spasms by feeding a diet which was poor in tryptophan. This would suggest that perhaps xanthurenic acid or some other abnormal metabolite is toxic to the brain.

Summary Evidence which suggested pyridoxine deficiency was found in 6 out of 12 patients with the syndrome of infantile spasms and mental deficiency in whom no cause for brain damage was known. In the 6 patients whose brain damage was the result of a perinatal insult there was no such evidence. In all the 10 patients given ACTH or a steroid there was a lower xanthurenic acid output after a tryptophan load, and this coincided with clinical and EEG improvement. It occurred whether the pre-treatment result was normal or abnormal and whether the ætiology was a perinatal insult or was unknown. This suggests that ACTH may improve the patient through increasing pyridoxine availability to the brain. The results of systemic pyridoxine administration to 3 patients show that there is no true pyridoxine deficiency.

Many loose ends remain and I have not answered the question of the ætiology of the condition in the cryptogenic group; nor have I given more than a clue to the mechanism of action of steroids and corticotrophin in this condition. However, such investigations as Cochrane's and ours make one hope that we are now moving into a fourth period in the history of this disorder, the period of biochemical investigation, for this appears to be the most promising field for the future.

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Section of Experimental Medicine and Therapeutics

President A C Dornhurst MD

Meeting February 14 1961

The Human Forearm as an Experimental Preparation

Professor A D M Greenfield (*Belfast*)

I propose to consider the use that may be made of the forearm in investigating certain aspects of cardiovascular control. I shall consider its advantages and limitations, and then illustrate its usefulness by three specific examples.

Advantages: The arteries and veins are easily accessible for sampling, injection or pressure measurement. Substances can be infused into the brachial artery at a rate and dosage sufficient to cause large changes in the circulation through the forearm without disturbing the circulation to the body as a whole. The nerves are easily blocked, and there are a fair number of people about with normal vessels whose arms have been sympathectomized for hyperhidrosis or unfortunately denervated in accidents. It is easy to expose the forearm to varying local temperatures, and to local pressures above or below atmospheric. It contains by volume about 60% of muscle and only about 13% of skin (Abramson & Ferris 1940, Cooper *et al.* 1955). It is a paired organ. Both forearms are normally perfused with blood of identical composition and at the same pressure: both are subject to the same nervous influences. Therefore, while one forearm is subjected to special treatment the other can be observed as a control, so that allowance can be made for any general disturbances of the circulation when the results of the local treatment are interpreted. Finally, the total forearm flow is easily, reliably and quickly measured, as often as six times a minute, by venous occlusion plethysmography (Greenfield 1960).

Limitations: The precision of many observations would be improved, and many others would become possible, if the forearm were supplied by a single artery, if the blood from the skin drained into a single vein and that from the muscles into another, and if these veins then united to provide a sampling point for mixed venous blood. Unfortunately material, and particularly perhaps vasodilator substances, injected into the brachial artery is not usually distributed uniformly to all parts of the forearm, and while some veins receive blood mainly from the skin and others mainly from the muscles, the sources of blood in the various veins almost certainly vary with the state of the circulation through the forearm. The circulation through the skin and the muscle of the forearm may not respond and react in the same way as that in the skin and muscle in other areas in the body.

I now propose to give three examples of ways in which, during recent years, observations on the forearm have illuminated our understanding of the regulation of the circulation.

(1) *The Control of Body Temperature*

It has been known for twenty-five years that when a person is heated, the blood flow increases through the forearm as well as through the hands and feet. In 1938 Grant & Holling showed that there are active vasodilator nerves to the skin of the forearm. When they heated a subject (the circulation to the hand being arrested to exclude disturbance from venous blood returning from the hand) there was a rise in temperature over normally innervated areas of the skin, but not over the areas of skin rendered anæsthetic by blocking the ulnar nerve. The rise in temperature indicating vasodilatation, therefore depended on activity in the nerves. Subsequent observations did not settle the question whether the skin vessels alone participate in the vasodilatation in the forearm or whether the muscle vessels also participate, until seventeen years later. It was then established that the increase in flow is confined to the skin, and that the muscle circulation remains almost or completely unchanged. We will now examine one of the pieces of evidence for this statement.

Fig 1 shows an experiment by Roddie *et al.* (1957*a*) in which the total blood flow through the forearm was measured by venous occlusion plethysmography. The subject was warmed up by

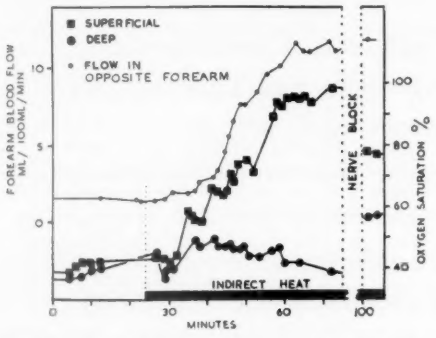

Fig 1 *The effect of heating the body on the total forearm blood flow, and on the oxygen saturation of the blood in superficial and deep veins, draining mainly skin and muscle respectively.* (*Reproduced from Roddie* et al., 1957a, *by kind permission*)

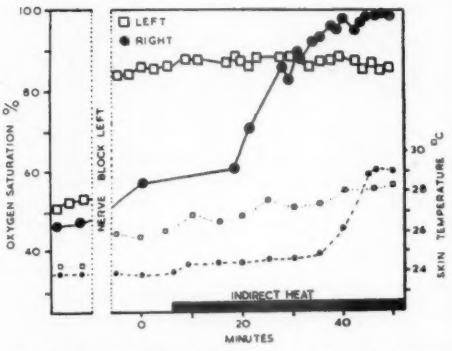

Fig 2 *The effect of blocking the nerves to the left forearm on the oxygen saturation of the superficial venous blood* (*large symbols*), *and skin temperature* (*small symbols*). *The effect of subsequent heating of the body is shown.* (*Reproduced from Roddie* et al., 1957a, *by kind permission*)

wrapping him in blankets and immersing the feet in hot stirred water. When he became hot, his total forearm blood flow increased.

To follow the changes in the skin and in the muscle circulation, fine catheters were inserted, in the manner devised by Dr Mottram, into deep and superficial veins, the former draining mainly muscle, the latter mainly skin. When the subject was heated, the oxygen saturation of the venous blood coming from the skin was greatly increased, but that of blood coming from the muscles was practically unaltered. If it is assumed that the oxygen consumption of skin and muscles remained substantially unchanged, this result indicates a greatly increased circulation through the skin, and an unaltered circulation through the muscles.

Other observations on the forearm by Edholm *et al.* (1956) and on the calf of the leg by Barcroft *et al.* (1955), using quite different techniques, led to the same conclusion.

At the end of the experiment in Fig 1 the nerves to the forearm were blocked. The total forearm blood flow was unchanged, but the venous oxygen saturations indicate a reduction in skin blood flow and an increase in muscle blood flow. Evidently, in the heated subject, the nerves to the skin were actively causing vasodilatation, as shown earlier by Grant & Holling (1938). The nerves to the muscle, on the other hand, were exerting a vasoconstricting influence, which body heating had failed to inhibit.

It is not possible to say, from the results of such an experiment, whether the increase in blood flow through the skin of the forearm is due entirely to nervous influences, or whether, in the heated person, a change in the pressure, quality or composition of the blood may be partly responsible.

A further experiment (Fig 2) clears up this question, and makes a further point about the increase in blood flow through the skin of the forearm when a person is heated. Blood was withdrawn from superficial veins of both forearms. The nerves to one forearm were blocked, and the oxygen saturation increased on that side. This indicated that, in the initially cool subject, there was activity in vasoconstrictor nerves to the skin.

The subject was then heated. The venous oxygen saturation remained unchanged on the nerve-blocked side. Evidently any changes in the forearm circulation cannot be explained by changes in the pressure or composition of the blood. In the normal forearm, the venous oxygen saturation first increased to equal that in the blocked arm; this increase probably indicates a removal of vasoconstrictor activity. It next increased to above the level in the blocked forearm. This indicated active vasodilatation. The increase from 85% to 96% saturation is not, at first sight, impressive, but it implies a very great increase in blood flow. The venous saturation, can, of course, only approach the arterial, however great the blood flow may be.

There is now an accumulating body of evidence to connect the vasodilatation in the skin of the forearm with sweating. The work of Fox & Hilton (1958) makes it very probable that the vasodilatation is in fact due to the release of the very active vasodilator substance, bradykinin, from the sweat glands. The nerves concerned are primarily sudomotor rather than vasomotor. Whether there are also directly acting vasodilator nerves is not yet clear.

We may summarize by saying that during body heating the muscle circulation is little changed in the forearm. The first small increase in skin

circulation is due to withdrawal of vasoconstriction activity. The second and larger increase is due to active vasodilatation, probably secondary to sweat gland activity.

(2) *Reflex Regulation of Vasoconstrictor Nerves to Muscle*

We have seen that there are vasoconstrictor nerves which normally exert a moderate vasoconstrictor effect on the blood vessels of the muscles of the forearm. There is plenty of other experimental evidence to support this conclusion. This vasoconstriction is removed by blocking the nerves, but is unaffected by general heating of the body. The question arises as to its normal purpose, and its normal reflex control. One answer to this question has been given by Roddie *et al.* (1957*b*). They observed that while the legs of a recumbent subject were raised, there was a considerable increase in the blood flow through the forearm (Fig 3). Measurements of oxygen saturation in venous blood indicated that the increase was through the muscles, not the skin (Roddie *et al.* 1956). Other experiments showed that the increase in flow is up to the level obtained by nerve block, and can therefore be accounted for by reduction in activity of the vasoconstrictor nerves.

Fig 3 shows that leg-raising caused a rise of central venous pressure, but little change in arterial pressure. This suggested that a raised central venous pressure is the effective stimulus, and this view was reinforced by the further finding that carotid arterial occlusion provoked scarcely any change in forearm vascular resistance, although it caused conspicuous reflex changes in heart rate (Roddie & Shepherd 1957).

It therefore seems likely that the vasoconstrictor control of muscle blood vessels is reflexly regulated by changes in central venous pressure. Such adjustments are probably of importance in hæmorrhage and perhaps in other conditions.

(3) *Response to Emotional Stress of Vasodilator Nerves to Muscle*

Vasodilator nerves to muscle blood vessels have been described in various animal species, and in the last fifteen years Folkow & Uvnäs (Eliasson *et al.* 1951, Uvnäs 1954) and their colleagues in Sweden have demonstrated that electrical stimulation of areas of the cerebral cortex and of the brain-stem is capable of provoking a profound vasodilatation in voluntary muscle, mediated through the sympathetic outflow and blocked by atropine. This system, however, is unaffected by

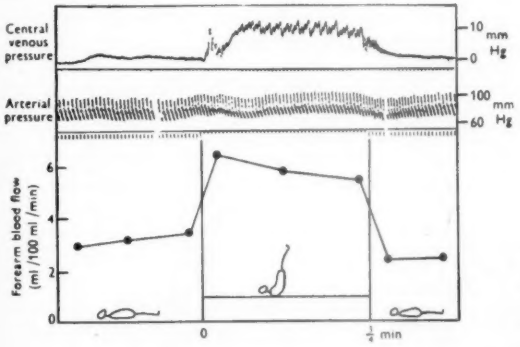

Fig 3 *The effect of raising the legs of a recumbent subject on the central venous pressure, the arterial pressure, and the blood flow through the forearm.* (*Reproduced from Roddie* et al., 1957b, *by kind permission*)

The increase in forearm flow was prevented if the circulation in the legs was arrested by a cuff while they were lifted up. This suggested that the effective stimulus was the influx of blood from the raised legs to the trunk or head. In agreement with this, the increase was greater when the legs and pelvis were raised, than when the legs alone were raised. Venous cuffing of the neck, to congest the venous system in the head, had no effect. This suggested that the stimulus was accumulation of blood in the trunk. This conclusion was reinforced by the finding that negative pressure breathing reproduces the effect of leg-raising (Blair, Glover & Kidd 1959).

stimulation of the baroceptor nerves, and other nerves which affect the vasomotor centre and provoke reflex changes in the vasoconstrictor outflow. No afferent pathway capable of reflexly affecting the vasodilator system was found.

It was, however, observed by Abrahams & Hilton (1957) that in conscious unanæsthetized cats electrical stimulation of areas of the brain that excite the muscle vasodilator system causes extreme agitation and all the signs of an emotional disturbance. This observation suggested to us that perhaps emotional stress was the effective natural stimulus for activating the muscle vasodilator system.

Up to two years ago the only evidence for muscle vasodilators in man was the observation of Barcroft & Edholm (1945) that during post-hæmorrhagic fainting the blood flow is, on average, greater through the intact than through the nerve-blocked forearm. It seemed worth while to test for muscle vasodilator nerves during emotional stress.

It has been know for twenty-five years that emotion causes an increase in total forearm blood flow, but the relative contributions of nervous and humoral control have not been defined.

Fig 4 shows an experiment in which the blood flow through the hand, and also that through the whole forearm, was measured, and the subject was emotionally stressed. This was done by carefully devised suggestion that there was a severe leak of blood round the arterial needle which had been placed in the brachial artery for pressure measurements. The total forearm flow increased to a high level, much higher than is caused by nerve block, and of the order seen immediately after exercise

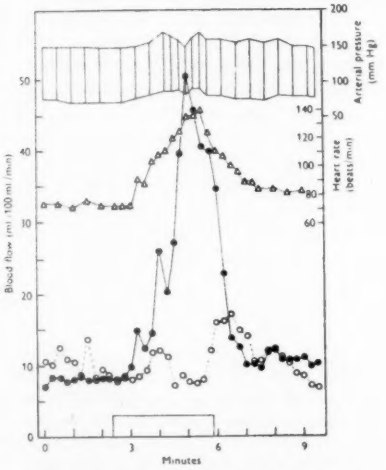

Fig 4 *The effect of severe emotional stress on the arterial pressure, heart rate,* △*; forearm blood flow,* ●*; and hand blood flow,* ○*. During the time represented by the rectangle it was suggested to the subject that he was suffering from severe blood loss.* (*Reproduced from Blair, Glover, Greenfield & Roddie,* 1959, *by kind permission*)

of the forearm muscles. The arterial pressure was little changed, so there was clearly an active vasodilatation, of either chemical or nervous origin, and in either skin or muscle or both.

The venous oxygen saturation was increased in the deep veins, but unaltered in the superficial veins, during the emotional stress. This showed that the vasodilatation was almost certainly confined to the muscle circulation.

Observations were made on a patient with normal vessels who had had a unilateral sympathectomy (by Mr T J Wilmot of Omagh) for Ménière's disease. The dilatation was confined to the innervated forearm, and therefore appeared, in this case at least, to be of nervous and not of humoral origin. The final question was whether the vasodilation was due to reduction of activity in vasoconstrictor nerves, or to an increase in activity in vasodilator nerves. This has already been partially answered by the observation that the flow may rise above the level caused by nerve block. To provide an independent check, atropine was infused into one brachial artery; given in this way it exerts its action mainly in the injected limb, and has relatively little action elsewhere. On now starting the emotional stress, the response was seen to be much reduced on the atropinized side. This indicated that the response was at least partially, and possibly wholly, mediated by a cholinergic mechanism.

This conclusion is in agreement with that reached by other workers, notably Barcroft *et al.* (1960). We can at present only speculate on the frequency with which this mechanism is activated in normal life, and on the advantages it may confer in meeting emergencies.

These three examples serve to show some of the ways in which the forearm may serve to analyse the way in which the circulation to skin and muscle is controlled, and the reflex stimuli determining the control.

It is unfortunate that, with the exception of the calf of the leg, the circulation to muscle in other areas cannot be as simply and precisely studied as that in the forearm. We are therefore, in the main, unsure whether or not the behaviour of the forearm is typical of that of muscle as a whole. We provisionally presume that it is, but this remains to be tested.

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Dr R F Mottram (*Oxford*) **and**
Professor W J H Butterfield (*London*)

The Human Forearm as a Preparation for Metabolic Investigations

Skeletal muscle accounts for 30–40% of body weight; its metabolic activity is thus an important fraction of that of the whole body. The veins of the human forearm are so arranged that it is easy to obtain samples of the blood leaving the muscle masses, without gross contamination with effluent blood from other sources. The measurement of A–V differences across the muscle, together with that of blood flow, enables the Fick method to be used for estimating quantities of substances used or produced by the muscle. These studies are easily performed in the conscious subject.

Fig 1 is a drawing made from a dissected antecubital fossa to show the connexion between deep and superficial veins which enables the sampling of muscle venous blood; twenty-two fossæ were dissected. No two were the same in appearance but in twenty-one a probe or catheter would have passed directly into a vena comitans of the radial, ulnar or interosseous artery. In one dissected fossa no deep branch was found.

The manufacture of fine polyethylene and nylon tubes has made it possible to insert a catheter into the penetrating vein and thus to sample blood directly from deep veins. Fig 2 shows the way in which the forearm is prepared for study, with a plethysmograph for measuring blood flow and a catheter in a deep vein.

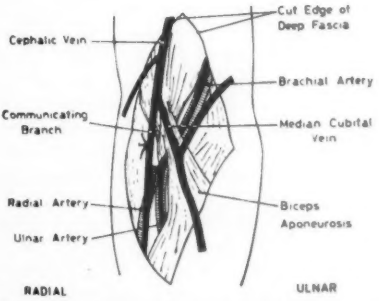

Fig 1 *A drawing of one of the dissected antecubital fossæ. The penetrating vein originates from a vena comitans of the radial artery and enters the median cubital vein just below the junction of the latter with the cephalic vein*

Before describing the results obtained by the various workers who have used this preparation, some of the objections and difficulties of the method must first be considered. The deep forearm veins drain tissues other than muscles. The returning blood from the hand is excluded by stopping all circulation to the hand. The small contributions from normal bone and from nerve, connective and adipose tissues cannot be avoided and the latter will be of importance in studying fatty acid metabolism. The blood may not be in equilibrium with tissue fluid or intracellular water. Thus during a glucose infusion a substantial part of the glucose leaving the arterial blood is passing only into the tissue fluid. If the rate of lactic acid production were to increase, some of this would be retained in cell and tissue fluid water, displacing CO_2 from the bicarbonates, thus producing a spurious rise in tissue R.Q.

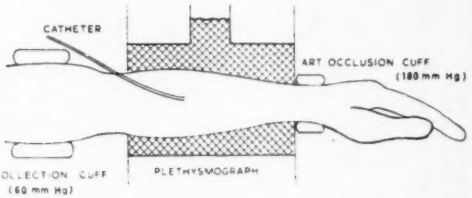

Fig 2 *A diagram of the arrangement of the arm with plethysmograph cuffs and intravenous catheter in place. The upper cuff is inflated to* 60 *mm Hg to measure blood flow and the lower one to* 180 *mm Hg to prevent the sampling of blood from the hand*

The objections and advantages of the principal ways of measuring blood flow are set out in Table 1. No method is ideal, though on balance I prefer the venous occlusion methods. The only method that can give a direct value of muscle blood flow is

Table 1
The advantages and disadvantages of the methods of estimating forearm muscle blood flow

Method	*Advantages*	*Objections*
Indicator dilution		
Continuous infusion	No extra equipment or punctures required	Measures whole forearm blood flow. Poor mixing of dye and blood. Hæmolysis. Analytical
Repeated injections	Measures flow in tissues studied	Rapid repetition of measurement is not possible
Venous occlusion plethysmography		
Water-filled plethysmograph	Frequent estimates are easily made. Constant local state	Measures whole forearm blood flow. Arm must be fixed. Sometimes uncomfortable. Measures flow while venous pressure raised
Witney strain gauge	Simple to apply. Freedom of movement	Whole forearm flow measured. Environmental constancy not achieved
Radioactive sodium and Hensel's needle	Measure of flow in muscle. Simple to run	Flow measurement not in ml. Flow measured in damaged tissue

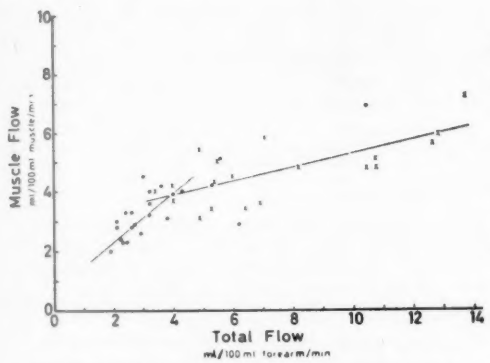

Fig 3 *The relationship between total forearm blood flow and muscle blood flow as calculated from the residual flow after adrenaline iontophoresis*

that of measuring an indicator concentration curve in the deep venous blood after a rapid arterial injection of indicator. A continuous sampling and recording system would be needed to make this a practicable method, together with a suitable indicator substance. It is obviously preferable, whichever of the other methods are used, to make some sort of allowance for the cutaneous component of flow. That based on the relationship between the total flow and that remaining after the iontophoresis of adrenaline into the skin is the most rational (Cooper *et al.* 1955; Edholm *et al.* 1956). Fig 3 shows the results obtained by these workers, total flow being plotted against muscle flow.

Apart from these fundamental objections to the techniques used in studying the metabolism of the forearm some practical difficulties have occurred. In threading a catheter upstream, valves are frequently encountered. If a valve is met in the communicating vein and the catheter tip lies outside it, then it is not possible to avoid contaminating blood samples with superficial vein blood. Difficulty occurs if the catheter tip lies in the sinus between the valve flap and the vein wall. Inserting the catheter into a superficial vein can be confirmed by palpation through the skin, but an X-ray is the only certain way of checking the catheter's position. If the tip lies in a large vein and is not close to a valve as much as 5 ml of blood can be withdrawn without hæmolysis in one minute.

Venous occlusion above the elbow might be thought to aid the sampling of blood, but it has been shown that when this is done blood from the superficial veins passes rapidly into the deep vessels and mixes with the samples (Coles *et al.* (1958).

In the majority of studies it is necessary to obtain arterial, or near-arterial blood. Sampling venous blood from a hand kept in hot water has been used. This gives results virtually indistinguishable from arterial blood, but may cause a rise in general body temperatures and consequently a vasodilatation in the forearm skin vessels.

Duplicate analyses less than 0·1 vol./100 vol. blood apart are easily obtained for oxygen. With an A–V difference of 5–10 vol.% the analytical error is $<4\%$ of the observed value. Nothing like this degree of accuracy can be obtained with glucose. 7·5 mg is chemically equivalent to 10 ml O_2. Duplicates less than 2·5 mg% are not easily achieved and the error is therefore large in proportion to the expected A–V difference in the fasting state. After a meal or after glucose the error becomes a much smaller proportion of the observed difference.

Having outlined these objections and difficulties, we can now consider what has actually been achieved with the forearm preparation, the work at present in progress and what might be done in the future.

Table 2
Muscle O_2 uptake as determined by different workers

Author	*Mean value ml/100ml muscle/min*	*Range*	*No. of observations*	*Remarks*
Holling (1939)	0·19	0·12–0·28	34	Water at 30° C, skin flow assumed nil
Mottram (1955)	0·24	0·09–0·54	174	Water at 34°C
Mottram (1958)	0·27	0·09–0·44	194	Water at 34° C
Andres *et al.* (1956)	0·27	0·15–0·43	?	Arm exposed to air at 25°C
Holling & Verel (1957)	0·28	0·20–0·36	20	Water at 34°C
Abramson *et al.* (1958)	0·21	0·11–0·32	68 approx.	Water at 32°C

Table 2 shows the results of O_2 uptake obtained by different workers. These have all been recalculated from the observed A–V differences and total flow by the method of Mottram (1955). It is notable that three sets of workers obtain almost the same result and that others, working with lower plethysmograph temperatures obtain lower values. In 1939, Holling did not use a catheter but advanced a needle tip from the median cubital vein as far as he could into the mouth of its penetrating branch. The O_2 uptake of the whole muscle mass of the body, using a value of 0·27 ml/100 ml muscle/min, is equivalent to 30% of that of the whole body, about the same as the combined O_2 uptake of gut and liver.

Mottram has used his results, in which 10–30 observations have been made on single forearms (but not all on one occasion), to investigate the

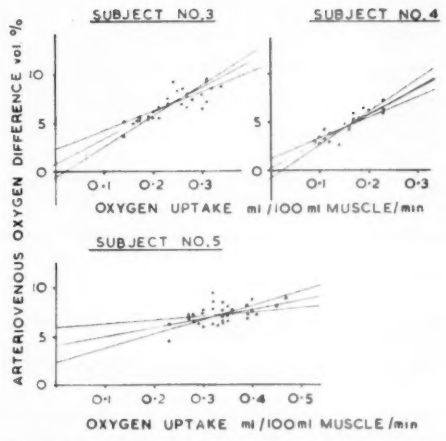

Fig 4 *The relationship between O_2 uptake and A-V O_2 differences in three forearms*

relationship between O_2 uptake and its two determinant parameters. He found first that O_2 uptake in any one arm was not constant and therefore that blood flow and A–V uptake did not vary inversely with each other, and secondly, that in 13 out of 16 arms O_2 uptake was related directly to A–V O_2 difference as is shown in Fig 4.

Mottram (1958) speculated concerning the minimum venous blood O_2 tension, below which diffusion of O_2 to the tissue would be deficient and arrived at a figure of about 20 mm Hg. Scherrer & Monod (1960) have found in the venous blood from working forearm muscle that the efferent blood pO_2 falls to and remains at this level, independently of the severity of the work done.

This forearm preparation is also being used to study many other aspects of the skeletal muscle metabolism, in fasting and in fed subjects, by day and over night. Table 3 shows values obtained in fasting state.

Table 3
The uptake or production of various substances by the forearm muscle

Substance	*Value /100 ml muscle/min*	*Authors*	*Remarks*
Potassium	26·5 μg	Andres *et al.* (1957)	16–20 hours post prandial
	nil	Andres *et al.* (1957)	Overnight
Phosphate	0·24 mg	Mills & Thomas (1959)	Approximately 4 hours after 'light' breakfast
Glucose	0·07 mg	Andres *et al.* (1956)	
	0·08 mg	Butterfield & Holling (1959)	
	0·15 mg	Brown & Mottram (1959)	
Lactic acid	0·04 mg	Andres *et al.* (1956)	
Nefa	−0·25 to +0·71 μEq.	Hanley (personal communication)	
CO_2	0·19 ml	Andres *et al.* (1956)	The R.Q. is 0·74

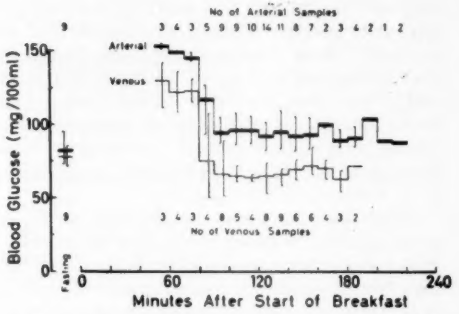

Fig 5 *Glucose A-V differences before and for three and a half hours following a large breakfast. The vertical lines are the range of values about the mean for each ten-minute period*

The basal state has been modified in various ways, and the effects on the metabolic behaviour of the muscle investigated.

Glucose uptake after a large breakfast was studied by Brown & Mottram (1959). Fig 5 shows the course of both arterial and venous levels during the three and a half hours following the meal. The most remarkable aspects are the sharp fall that occurs in both levels one-and-a-half hours after a meal, the large size (up to 60 mg%) of the A–V difference at this time and the depression of venous blood glucose below the fasting level. There may be little further change in arterial level for two hours following the drop at one and a half hours.

It has also been measured during an infusion of glucose, though in this case the calculation included passing from blood into the tissue fluid space. Brown *et al.* (1959) estimated the

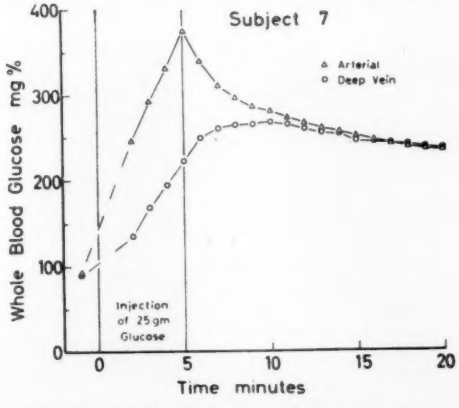

Fig 6 *Arterial and muscle venous glucose concentration after rapid intravenous injection of 25 g glucose*

amount that entered this space after a rapid injection of glucose (Fig 6). During the first ten to twenty minutes after the injection started the A–V differences were up to 200 mg%, but by the end of this time had fallen to the fasting level, and afterwards to zero. Most of the glucose that left the blood in the forearm had entered the tissue fluid space. The later muscle uptake proceeded at 0·6–1·0 mg/min/100 ml muscle.

Other lines that have already been started include the effect of the adrenal cortex hormones on PO_4 and glucose uptakes (Mills & Thomas 1959), the effect of insulin on glucose uptake (Hardwick *et al.* 1959) and some of the effects of local muscular exercise.

In this method we thus have a tool which has already been used to study some aspects of human tissue metabolism *in vivo*, and with which much more work can be performed.

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Meeting March 17 1961

Clinico-pathological Significance of Renal Biopsy

A Joint Meeting with the Renal Association was held taking the form of a Public Report Session following the Ciba Foundation Symposium on the above topic. The opening speakers were Professor A R Rich (Baltimore), Dr R L Vernier (Copenhagen), Professor J Hamburger (Paris), Dr C Brun (Copenhagen), Professor D P Earle (Chicago) and Professor R Kark (Chicago).

A full report of the meeting will appear as part of the 'Ciba Foundation Symposium on Renal Biopsy' (London, in press).

Section of Surgery

President
Professor Lambert C Rogers CBE VRD FRCS

Meeting February 1 1961

(*continued from June 'Proceedings' p 492*)

Dissecting Aneurysm of Aorta

by L P Thomas MCh FRCS (*Cardiff*)

Acute dissection of the thoracic aorta is a subject receiving considerable attention from surgeons at the present time and there have been three communications to the Society in the past two years. I wish to discuss the management of 4 cases which have been treated by operation.

The ætiology of the condition is uncertain, but splitting of the aortic wall in this condition resembles separation at the medial layer during thrombo-endarterectomy for arteriosclerosis. It is probable that in the hypertensive subject tearing of the intima occurs, blood enters this plane and produces extensive stripping.

The diagnosis should be established as early as possible. The occurrence of severe chest and back pain in a hypertensive subject is highly suggestive. The presence of altered peripheral pulses is often emphasized, diminution or absence of carotid pulsation may be associated with signs of cerebral ischæmia. I have found that diminution of the femoral pulse does not remain constant but varies hourly. It implies that dissection has reached the iliac vessels, an important observation when surgery is contemplated Full, bounding pedal pulses have been observed in several cases, a strange sign in a shocked patient.

The ECG may show no significant abnormality, and thus be useful in excluding coronary thrombosis, however the changes of a posterior infarct may indicate that dissection has extended back into the pericardium or myocardium. Radiology of the chest by plain films (Fig 1), tomography and screening demonstrate widening of the aortic shadow, its outline being blurred. Aortography by percutaneous catheterization of the femoral artery is the most satisfactory way of demonstrating the extent of the dissection (Sutton 1960). There is characteristic narrowing of the true lumen with widening of the aortic wall shadow. The opaque medium rarely enters between the layers.

Normal serum transaminase levels are usual and help in excluding coronary thrombosis. A raised level may occur with extension of the dissection into pericardium or myocardium (Adams & Jacoby 1960). Congestion of the liver from cardiac failure and renal failure may also cause raised values.

Surgical treatment is indicated for the majority of cases surviving the first twenty-four hours; a

Fig 1A **Case 1** *demonstrating widening of aortic outline before operation*

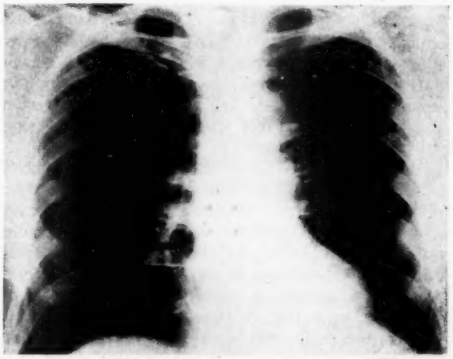

Fig 1B *Three months after operation, slight widening of aortic outline persists. It remains the same one year later*

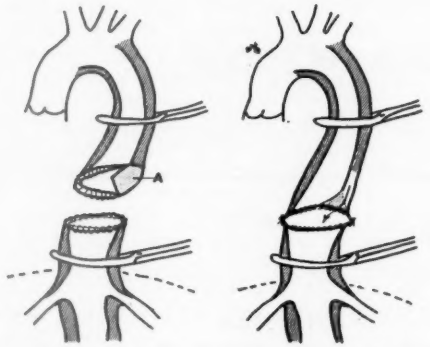

Fig 2 *Diagram of fenestration operation described by De Bakey. The area of intimal resection is shaded A*

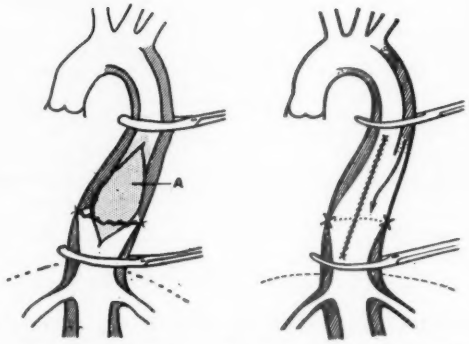

Fig 3 *Diagram of type of operation performed on Case 3; the intimal area A was removed through a longitudinal incision. Circumferential suturing prevented further distal dissection. A similar procedure was performed in the abdominal aorta in Cases 1 and 2*

significant proportion do so with a latent period of one to five days before further dissection or rupture of aorta. Operation is contraindicated for extension of dissection into the pericardium or myocardium; cross-clamping of the thoracic aorta in these cases often precipitates massive rupture and cardiac tamponade.

De Bakey (De Bakey *et al.* 1955) advocated transection of the lower thoracic aorta, the construction of an intimal opening and resuture of the aorta to prevent further dissection (Fig 2) and has recorded 27% mortality in 36 cases (De Bakey 1958).

The procedure has been modified by making a longitudinal incision in the aortic wall and a large intimal opening varying in size from 2×4 cm to 6×4 cm. Distal dissection is prevented by circumferential suturing (Fig 3).

Of the following 4 cases 2 survive.

Case 1 Male aged 47. Known hypertensive eighteen months, with headaches and mild hemiparesis six months previously. Severe back and chest pain, accompanied by vomiting on day of admission when blood pressure was 170/100. Right femoral pulse weaker than left at times. ECG and serum transaminase levels normal. Chest radiograph showed widening of thoracic aorta. Abdominal aortic fenestration performed five days after admission on January 25, 1960, with relief of pain. Patient alive and fully employed one year later, chest radiograph still shows slight widening of aorta shadow.

Case 2 Female aged 58. Sudden onset of severe headache and chest pain six months previously. Recurrence of chest and back pain with radiation to legs on day of admission. Blood pressure 169/100. Right femoral pulse weaker than left. ECG and transaminase levels normal. Chest radiograph showed widening of aorta. Aortogram confirmed dissection of thoracic aorta extending to aortic bifurcation. Abdominal aortic fenestration performed same day with relief of pain. Symptom free when seen six months later.

Case 3 Male aged 63. Known hypertensive (190/100) for several years, on drug therapy. Sudden severe chest pain on day of admission to local hospital. Patient shocked, blood pressure 100/70. ECG normal. Chest X-ray showed widening of aorta. Thoracic aortic fenestration under hypothermia performed on second day, with construction of opening 6×4 cm. Good recovery with relief of pain. Sudden death six weeks later from rupture of outer layer into pleural cavity. Blood pressure then 170/100, patient was not receiving hypotensive drugs. Autopsy showed fenestration to be patent.

Case 4 Female aged 62. Known hypertensive for four months (220/110), treated with drugs. Pain in head, neck and chest two days before admission. Unconscious for three hours, right carotid pulse absent, left hemiplegia present. Chest radiograph showed very wide aortic shadow with pleural effusion. Serum transaminase (SGOT) 46 units. Thoracotomy revealed aortic dissection involving the arch of aorta, intrapericardial blood was present. Clamping of the aorta when blood pressure was 90/50 was followed by sudden rupture into pericardium with tamponade and death.

Comment: The advisability of employing the thoracic approach is questioned. Most surgeons have advocated fenestration in the thoracic aorta near the intimal tear so that the pressure is lowered in the outer layer to lessen the risk of rupture. It is apparent from the third case that this does not always occur; autopsy six weeks after operation showed rupture of adventitial coat just above a large patent intimal opening.

Rob & Kenyon (1960) reported 5 cases of aortic dissection; the abdominal approach was used in 3 and thoracic in 2. The 2 survivors in my group have both had an abdominal approach. I feel that this may yet prove to be the better operation provided, of course, that the dissection has extended into the abdominal aorta; this occurs in about half the cases. Examination of pulses and aortography helps to demonstrate the lower level of dissection.

Cross-clamping of the aorta at the thoracic level produces a dangerous hypertension which may lead to rupture of the dissection into pericardium as in Case 4. Arfonad was given to lower the systolic pressure to 90 mm Hg before applying clamps. Occlusion of the aorta above the diaphragm may result in renal and spinal cord damage if it is maintained for over one hour, and I find it difficult to complete the fenestration in a shorter time. The induction of hypothermia offers protection; it was used in 2 cases but it involves an extra hazard for the patient.

Control of hypertension in the post-operative period is most important and a level of about 150/90 should be maintained with the use of drugs such as Ansolysen. It is significant that this step was omitted for Case 3 who died of aortic rupture in the sixth week when the pressure was 170/110.

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DISCUSSION

Mr Peter Martin (*Chelmsford*) said that though he had been interested in dissecting aneurysms for some time his experience had been limited as he had seen but 6 patients with the condition, and operated on only 3. He had also had the opportunity of examining some others at autopsy.

There are two points he wished to make about the diagnosis. (1) It seemed that ECG changes suggesting a posterior myocardial infarct were common when a dissecting aneurysm and no infarction was present. This might obscure the diagnosis and had in fact done so in one of his patients. (2) Changing distal pulses were pathognomonic of dissecting aneurysm. For example, the right femoral pulse might be absent, but at examination a short time later the right might be present and the left absent.

The surgical treatment of dissecting aneurysm in the main mimicked nature by creating a port of re-entry from the extraluminal back into the intraluminal channel of the aorta. Of the 3 patients he had operated on one was living and well eighteen months afterwards, one returned to work but died a year to the day after operation and the third died ten days after operation. Both those who died, did so from intrapericardial rupture of the outer layer of the extraluminal channel, this channel being patent throughout its course. The third and living patient was one with a chronic dissecting aneurysm. In the post-mortem specimens he had seen, the extraluminal channel had always been patent. In all the cases he had seen death had occurred from rupture of the outer layer of the false channel.

Rupture of the extraluminal channel was just as likely to occur whether there was a port of re-entry or not. It was said that the natural recovery rate of dissecting aneurysm was 20 to 25%. He wondered if patients subjected to surgery might not well have survived had they been treated conservatively. Possibly hypotensive drug treatment might be best for those who survive the initial catastrophe.

The Control of Disseminated Breast Cancer

by Owen Daniel MS FRCS (*Rhyl*)

There are, in common use at the present time, many different ways of attempting to control disseminated breast cancer by hormonal methods. But not one of these does more than give merely temporary respite to at best some 50% of patients and each may be followed by unpleasant, or even dangerous, side-effects and complications. It is therefore not surprising that the history of the evolution of endocrine therapy of breast cancer is one of waves of enthusiasm, followed by disillusionment and rejection, and that even to-day it is difficult to decide what advice to give the individual patient.

It is also apparent that, until new and better forms of treatment become available, the most urgent requirement is to find means of selection so that existing methods, especially those of a major character, are offered only to those patients who are likely to benefit and that the others are spared the distress of unsuccessful treatment.

This paper reports the results of certain investigations into this problem. The basic plan of the investigation was to study the response of individual patients to the successive administration of testosterone, oophorectomy, stilbœstrol, corticosteroids and finally either adrenalectomy or hypophysectomy, in order that response to the major forms of therapy could be related to response to the simpler procedures. In all 112 women have been under observation and the majority followed to the inevitable termination. Of course no patient received each of the treatments mentioned but all had at least three and many four or five different types of treatment. In each case treatment was changed only when it was ineffective and when symptoms demanded relief. At the time of change all hormone administration was discontinued for ten to fourteen days before starting the new regime.

The results have been classified as effective or ineffective according to the following criteria:

Treatment was considered to be effective if it induced, for a period of more than two months, both worth-while subjective relief and unequivocal objective evidence of regression of the disease, as shown for example by regression of cutaneous lesions or radiological evidence of improvement in bone or lung metastases. Treat-

ment was considered ineffective if it exercised a beneficial effect for less than two months, or if it failed to do any good, or if response was mixed – that is if regression of one lesion was accompanied by progression of any other manifestation of the disease. In other words treatment was regarded as effective only when the beneficial results were unequivocal, of reasonable duration, and indeed readily appreciated by all concerned.

The main points that have emerged are:

First, in 50% of all women breast cancer is completely resistant to all forms of endocrine therapy. A similar claim was made by Huggins & Dao in 1954, but other workers have cast doubt on this rigid classification because it is known, for example, that failure to respond to œstrogens, or androgens, may be followed by improvement after adrenalectomy or hypophysectomy (Strong *et al.* 1956). The second point is the fundamental importance of ovarian function on the effects of hormone therapy, a factor which is readily apparent in the observations made during the course of this study.

Testosterone proprionate was administered by intramuscular injection, in doses of 100 mg, three times a week, to 32 pre-menopausal women but was effective in only 7 (21%) of these, and in 2 appeared to induce an exacerbation, although in every case testosterone was quickly effective in suppressing menstruation. Testosterone was also given to 33 women who were two or more years past the natural menopause and proved effective in 12 (36%). Testosterone was thus effective nearly twice as often after, as it was before, the menopause. The main disadvantages of treatment by androgens are that the most effective preparations must be given by injection and that some 70% of subjects develop hirsuties and change in voice. Nausea and vomiting may also occur. Many patients will bear these unpleasant side-effects with fortitude, but the others are profoundly distressed and for this reason and also because, as will be shown later, oophorectomy appears to be better than testosterone for the younger women and stilbœstrol for the older women, I have now abandoned the use of testosterone.

Oophorectomy was performed on 70 patients and proved effective in 27 (45%) of the 60 of those who were pre-menopausal. Only once did death follow within a month of operation and this in a woman who was virtually moribund beforehand from pulmonary metastases. The only unpleasant side-effects were menopausal symptoms, which occurred in 7% of the subjects. In 30 out of the 60 of these young women, menstruation had ceased following the administration of testosterone and in another 7 menstruation had ceased following external irradiation of the ovaries. But in both groups the operation was as effective as it was in the other previously untreated pre-menopausal women, suggesting that ovarian function persists despite the fact that testosterone, or external irradiation, readily suppresses menstruation. Oophorectomy was performed on ten women who were four or more years past the natural menopause and in each of these was ineffective.

Stilbœstrol was administered in doses of 5 mg three times a day to 42 women who were two or more years past the natural menopause and was effective in 15 (35%) of these. The only harmful effects were nausea and vomiting which occurred in 3 of the 42 patients and fluid retention which appeared to precipitate congestive heart failure in one patient. The nausea and vomiting responded to the administration of chlorpromazine or anti-histamine drugs. At the start of the investigation stilbœstrol was given to 9 pre-menopausal women but in each case was ineffective and indeed appeared to produce an exacerbation in one woman. Its use for pre-menopausal patients was therefore abandoned, especially as other reports of its ineffectiveness in young women appeared at this time (Foss 1956, Lewison *et al.* 1956).

Prednisolone was administered to a group of 45 women. The regime employed was to give 20 mg twice a day for ten days and then reduce each dose by 5 mg every other day until a maintenance level of 5 mg twice a day was reached. Ten out of the 45 women were pre-menopausal and not one of these was benefited in any way, but of the 35 women in whom ovarian function had ceased following oophorectomy, or the natural menopause, 15, or nearly 43%, gained worth-while benefit which in many cases lasted as long as two or three years.

In addition to producing objective signs of improvement, in 43% of post-menopausal patients, prednisolone had a mild euphoric and tonic effect on almost all patients. The drug is easy to take and in the above doses seldom produced 'moon face' or other side-effects. The greatest danger was that after prolonged administration signs of acute adrenal insufficiency followed sudden withdrawal or severe stress such as an operation or acute infection. Only 2 patients complained of dyspeptic symptoms and both responded to the administration of alkalies and to a change to enteric coated tablets.

Combined bilateral adrenalectomy and oophorectomy, according to published accounts of large series, affords worth-while relief to some 47% of patients (Hadfield 1959). The operation is technically satisfactory and carries a low mortality,

but it is nevertheless a painful procedure for the patient and many surgeons are reluctant to undertake such a major operation when faced with a less than fifty-fifty chance of substantial benefit. It therefore seemed important to discover to what extent the beneficial results were due to oophorectomy, how much to physical removal of the adrenal glands and how much to the corticosteroids which must be given to maintain life following operation.

In an attempt to answer these questions 12 pre-menopausal women were submitted first to oophorectomy, later to corticosteroid therapy and finally to surgical removal of the adrenal glands. The results showed that under these circumstances surgical adrenalectomy was valueless as it added nothing to the benefits already obtained, irrespective of whether or not oophorectomy and steroid therapy had proved effective. Furthermore, the results of combined oophorectomy and steroid therapy in our hands, as well as those of others (Brinkley & Pillers 1960), are about the same as those which have been reported from combined bilateral adrenalectomy and oophorectomy. For these reasons it would appear that adrenalectomy can now be abandoned as a form of therapy for breast cancer.

Surgical hypophysectomy has been reported as yielding 48% of beneficial results in large series of patients (Hadfield 1959). But this operation can be technically difficult and unsatisfactory in so far as it often fails to ensure complete ablation of the gland, and is furthermore attended by a not inconsiderable mortality and morbidity so that here again there is an understandable reluctance in recommending the procedure and a real need for a satisfactory method of predicting the outcome. Eighteen of the women in the present series were submitted to surgical hypophysectomy. Five of these were pre-menopausal and 13 post-menopausal. The operation was effective in 8 patients and ineffective in 10. But the point of interest is that hypophysectomy proved effective only in those in whom the disease had been found endocrine-dependent as judged by response to prior oophorectomy and steroid therapy in the younger women, or stilbœstrol and steroid therapy in the older women. Hypophysectomy was ineffective in those women in whom the tumour was uninfluenced by the other forms of endocrine therapy.

These results could be summarized as follows: (1) In 50% of all women breast cancer is completely resistant to all forms of endocrine therapy. (2) Ovarian function has a profound influence on the effects on breast cancer of testosterone, stilbœstrol, oophorectomy and corticosteroids.

(3) Prednisolone is a valuable therapeutic agent for breast cancer, provided that ovarian function has ceased.

(4) The primary treatment of choice for disseminated breast carcinoma is oophorectomy followed by prednisolone, for the pre-menopausal woman, and a combination of stilbœstrol and prednisolone, for the post-menopausal woman.

(5) Adrenalectomy adds nothing to the benefits obtained from the above forms of primary treatment but hypophysectomy may give further worth-while relief to women in whom the tumour has proven responsive to the primary endocrine therapy. The regime described is both simple and humane and furthermore provides a useful means of selecting patients who are likely to benefit from hypophysectomy.

This work was done in the University Department of Surgery, at the Royal Infirmary in Sheffield. I am indebted to my former colleagues for referring many of the patients and to Mr Anthony Jefferson for performing the hypophysectomies.

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Film: Bilateral Adrenalectomy and Oophorectomy Through a Single Incision

Donald Barlow MS FRCS (*London*)

The film was made, at the Luton and Dunstable Hospital, to demonstrate the technical ease with which the combined operation can be performed through a single paramedian incision. Obesity was no bar to the operation.

Special points in technique were: (1) Division of the ligamentum teres. (2) The exposure of the left adrenal gland and protection of the spleen by a new technique termed the 'splenic hood'. (3) Access to the more difficult right adrenal gland by ligation and division of the accessory hepatic veins, liver retraction, and digital retraction laterally of the adrenal to expose the very high adrenal vein.

The film won an award at the first British Film Festival in London.

Meeting January 4 1961

Discussion on Non-penetrating Injuries of the Chest and Abdomen [*Abridged*]

Mr H R S Harley (*Cardiff*)

The Causes of Respiratory Failure in Closed Crush Injuries of the Chest and Upper Abdomen

Respiratory failure is important after these injuries and is a principal cause of death. Because the upper abdomen lies within the thoracic cage its contents are often damaged, and for this reason I have chosen the term 'crush injuries' of the chest and upper abdomen.

Arnott (1960) defines respiratory failure as 'that condition in which the amount of oxygen and carbon dioxide in the blood-stream is altered by an abnormality of the respiratory system'. Respiratory insufficiency will be used in the same sense. The Ciba Guest Symposium (1959) gives the upper limit of Pa_{CO_2} as 47 mm Hg, and the lower limit of Pa_{CO_2} as 75 mm Hg and of oxygen saturation as 93%, but these limits may be too rigid for elderly patients.

Respiratory failure may arise from an upset of ventilation, of diffusion or of distribution of gas and blood to the alveoli, e.g. the ventilation of imperfectly perfused alveoli, which increases the dead space effect, or the perfusion of imperfectly ventilated alveoli, which may cause hypoxæmia by creating a pulmonary arteriovenous shunt – the venous admixture effect. Inadequate alveolar ventilation results in asphyxia, whereas deficient diffusion and deficient ventilation of well-perfused alveoli cause hypoxæmia, with only slightly raised, normal or low carbon dioxide tensions in the arterial blood. Injuries of the chest may occasion any or all of these upsets, and if respiratory insufficiency is present then its treatment must take precedence over all other conditions except massive hæmorrhage.

The following classification of respiratory failure following injury is recommended: I. Respiratory failure due to impaired ventilation: Ventilation failure: (*a*) central. (*b*) peripheral. II. Respiratory failure due to impaired diffusion: Diffusion failure. III. Respiratory failure due to ventilation–perfusion inequality: Gas-blood distribution failure, or, more simply, distribution failure.

I. Ventilation Failure

Many factors conspire to cause ventilation failure after severe injuries of the chest and these may be conveniently classified into central and peripheral.

(A) CENTRAL VENTILATION FAILURE

This results from depression of the respiratory centre by alcohol, damage to the brain, sedatives, especially morphine, anæsthetics, or the development of circulatory failure. As Donald (1960) pointed out, central failure is easily overlooked for it causes weak respiratory movements without dyspnœa, which contrast with the powerful dyspnœa of frustrated respiration associated with peripheral failure.

(B) PERIPHERAL VENTILATION FAILURE

A number of conditions may combine to cause peripheral ventilation failure. The following are important:

Peripheral Ventilation Failure due to Deficient Movement of the Chest Wall

(1) *Paradoxical chest wall movement:* Proctor & London (1955) define paradoxical respiration as 'movement of the chest wall in a reverse direction from normal'. During inspiration the floating segment is sucked inwards and during expiration it is pushed outwards. Total ventilation is greatly reduced, as in an open pneumothorax. Furthermore the respiratory variations of pressure are greatly reduced in the paradoxical region so that gas is aspirated from it to the non-paradoxical areas during inspiration, the reverse occurring during expiration. This greatly increases dead space ventilation and further reduces alveolar ventilation in the non-paradoxical regions. Paradox also prevents effective coughing, and, by reducing or abolishing the negative pressure developed in the chest during inspiration, embarrasses diastolic filling and minute output of the heart, and so promotes circulatory failure.

Severe paradox must be corrected forthwith by methods which permit maximum ventilation while correcting deformity. The more a patient hyperventilates the worse becomes his paradox and his ventilatory failure. A vicious cycle is created. It is common for slight paradox later to become severe when other factors increase the ventilatory efforts.

(2) *Pain:* Pain produces ventilatory failure by preventing deep breathing and causing reflex, rapid, shallow breathing. The nearer dead space volume approaches tidal volume the less efficient is alveolar ventilation, which is the product of respiratory frequency and the difference between

the tidal and dead space volumes. Rapid, shallow breathing thus leads to alveolar hypoventilation. Pain must be relieved, but without drugs which depress the respiratory centre or strapping which restricts ventilation. Pain also renders coughing ineffective.

(3) *High paretic diaphragm:* After crush injuries of the chest the diaphragm takes up a mid-position, loses much of its mobility and, on an inspiratory X-ray film, appears to be elevated. This is probably reflex in origin due to pain.

Peripheral Ventilation Failure due to Pulmonary Tamponade

This term includes all conditions which reduce the capacity of the pleural space, so causing pulmonary compression collapse and impairing alveolar ventilation. These conditions include pneumothorax, hæmothorax, gastrointestinal ileus and diaphragmatic hernia. Barrett (1960) gives useful advice on the diagnosis of traumatic pneumothorax and hæmothorax.

Gastrointestinal ileus and diaphragmatic hernia are often overlooked. These (Barrett 1960, Virshup 1960), together with damage to the liver and spleen, are important complications, and this is why the term 'crush injuries' of the chest and upper abdomen is considered to be appropriate. Gastric and intestinal ileus may seriously embarrass respiration, and their development should always be anticipated. Herniation of abdominal contents through a ruptured diaphragm, usually on the left side, may result in alarming or fatal asphyxia.

Peripheral Ventilation Failure due to Airway Obstruction

Airway obstruction is an important cause of ventilatory deficiency after chest injuries. Its many causes include blood derived from intra-alveolar hæmorrhage, pulmonary œdema transudate, the secretions of bronchial mucous glands, inhaled vomit or other foreign material such as blood, and reflex bronchial spasm. It is especially likely to occur when head injury has rendered the patient unconscious, has depressed his respiratory centre, or has resulted in 'neurogenic' pulmonary œdema.

Traumatic pneumonopathy: In order to appreciate fully the importance and significance of airway obstruction one must understand the reactions that may occur in the lung and bronchial tree as the result of trauma. Much has been written about traumatic 'wet lung' (Burford & Burbank 1945, Harper & Tait 1946, Brewer *et al.* 1946, Daniel & Cate 1948, Griffiths 1960) and pulmonary œdema (Barrett 1960, Visscher *et al.* 1956). Traumatic pneumonopathy is a better name, for it represents a complex reaction to injury characterized by several widely different pathological processes.

Daniel & Cate (1948) showed that injury of the chest wall of dogs resulted in alveolar rupture, with extravasation of blood into the air spaces, comparable to that of experimental blast injuries in water (Clark & Ward 1943) or in air (Hooker 1924, Zuckerman 1940, Williams 1942). This occurred chiefly in relation to the chest wall injury, and in severe cases in the posterior part of the opposite lung also. Macroscopic hæmorrhagic consolidation varied from slight to a change resembling the consistency of liver. In addition to this there was widespread patchy interstitial and alveolar œdema of both lungs, which became diffuse if sodium chloride was infused. Similar widespread œdema could be induced by infusing hypoxic dogs, but hypoxia alone did not cause it. The blood and œdema fluid enter the alveoli and small bronchi producing areas of lobular collapse and alveolar hypoxia which may spread and become confluent. Similar changes were reported in human lungs after fatal accidents by Griffiths (1960), and have also been observed by the writer.

Daniel & Cate (1948) attribute œdema in the hæmorrhagic areas to irritation of the lung tissue by blood (Harper & Tait 1946, Pattle 1956) combined with the effects of hypoxia (Landis 1928, Drinker & Warren 1943, Drinker 1945), but they thought that œdema elsewhere was caused by nervous reflexes from the chest wall mediated by the vagus.

Visscher *et al.* (1956) in an exhaustive study showed that the immediate determinants of pulmonary œdema are the hydrostatic pressure gradient and the colloid concentration gradient across the capillary wall, the filtration area and the colloid permeability of the capillary wall, and the hydrostatic pressure in the draining lymphatic vessels. Many remote mechanisms may alter one or more of these determinants. Thus irritation of the medullary centres by injecting fibrin into the cisterna magna (Cameron & De 1949) causes generalized systemic vasoconstriction, systemic hypertension, and redistribution of blood to the pulmonary circulation. This both increases the filtration area of the lung capillaries, and causes the left ventricle to raise its diastolic pressure in order to expel its contents, with consequent elevations of pulmonary venous and capillary pressures of up to 70 mm Hg (Sarnoff & Sarnoff 1952). Raised intracranial pressure probably elevates the pulmonary capillary pressure by producing vagal bradycardia (Campbell *et al.* 1949, Visscher *et al.* 1956). Inspiratory and expiratory resistance cause acute pulmonary œdema experimentally by raising the pulmonary capillary pressure (Landis 1928, Luisada 1946, Reichsman 1946, Zinberg *et*

al. 1948, Haddy *et al.* 1950), and dyspnœa may also be a factor (Drinker 1945).

Upsets to the vagus may act by increasing airway resistance (Lorber 1939*b*, Reichsman 1946, Visscher *et al.* 1956) due to bronchospasm, bronchorrhœa, and altered mechanics of breathing, or by altering the permeability of the lung capillaries (Schiff 1894, Faber 1937). Hæmodynamic redistribution of blood and respiratory obstruction have both been incriminated as the chief cause of acute pulmonary œdema after experimental bilateral vagotomy. That these are not the only causes is indicated by the fact that bilateral vagotomy can cause acute pulmonary œdema despite tracheotomy (Schiff 1894, Lorber 1939*a*) to eliminate laryngeal obstruction, intermittent positive pressure respiration at normal depth and rate to avoid abnormal respiratory rhythms, and section of the cervical cord at C7 to cut off all sympathetic connexions between the brain and the circulatory system (Borison & Kovacs 1959). Furthermore, lesions of the vagal nuclei can produce acute pulmonary œdema in animals without causing any change in the rate or depth of breathing (Borison & Kovacs 1959), while sufferers from bulbar poliomyelitis who die with pulmonary œdema invariably have damaged vagal nuclei (Baker 1957). Vagal reflexes from the damaged chest wall may, therefore, play a part in promoting pulmonary œdema.

Hypervolæmia induced by intravenous infusions of blood or saline produces pulmonary œdema in the experimental animal by increasing the pulmonary blood volume and causing relative left ventricular failure, so raising the pulmonary capillary pressure (Altschule & Gilligan 1938, Opdyke *et al.* 1948, Doyle *et al.* 1951, Haddy *et al.* 1950). This effect is accentuated by hypoxia (Drinker 1945, Daniel & Cate 1948, Courtice & Korner 1952). Drinker (1945) considered that hypoxia acts by increasing the permeability of the lung capillaries, but the work of Visscher *et al.* (1956) indicates that it does so by producing heart failure. The only factors which have been proved to increase capillary permeability are certain poisons such as phosgene and thiourea derivatives.

Many of the above factors could act in producing pulmonary œdema after injury, and in addition the injury itself might play its part. Severe and sudden compression of the chest might injure the left ventricle, and cause it to fail. Bruising of its walls is sometimes seen at autopsy. Alternatively the abrupt rise of pressure, especially if the glottis be closed, might inflict generalized microscopic damage upon the pulmonary capillaries, perhaps aggravated by histamine release, causing them to dilate and to become permeable to protein, with resulting œdema. Since gross macroscopic damage to the lungs, major bronchi and trachea may result from crushing injuries, even without rib fractures, this suggestion seems reasonable.

Thus many factors, neurogenic, hæmodynamic, chemical and mechanical, may combine to cause generalized œdema of the lungs after injuries to the chest. These must be eliminated as quickly as possible for the condition may arise with alarming rapidity.

In addition to hæmorrhage and œdema fluid, excessive bronchial secretion and bronchoconstriction, consequent upon vagal reflexes (De Takats *et al.* 1939, De Takats *et al.* 1942), may be excited by the chest wall injury so increasing the amount of fluid in the lungs and narrowing the respiratory passages. De Takats *et al.* (1942) demonstrated bronchospasm by bronchography in dogs after blunt injuries of the chest wall, even when ribs were not fractured.

Another important factor concerned in airway obstruction is inability to cough effectively. This may be due to pain, to paradox, which prevents effective expulsive effort, or to depression of the respiratory centre by any of the mechanisms previously mentioned.

It is often assumed that the only cause of traumatic 'wet lung' is ineffective coughing, but the evidence indicates that certainly two, and probably three, factors are at work. These are excessive production of liquid (intra-alveolar hæmorrhage, pulmonary œdema transudate and reflex bronchorrhœa), inability to remove this excess, because of inadequate cough, and probably also narrowing of the bronchi by reflex spasm. It is this complex combination of conditions which constitutes traumatic pneumonopathy.

Traumatic pneumonopathy causes ventilation failure not only by obstructing the airways, but also by stiffening the lungs, which increases ventilatory effort and paradox, and by creating rapid shallow breathing, which impairs alveolar ventilation. It also leads to diffusion and distribution failure (*vide infra*).

Traumatic pneumonopathy is often complicated by infection for several reasons: (i) Pulmonary œdema fluid is rich in protein and is absorbed only slowly by the lymphatics (Courtice & Phipps 1946). Harford & Hara (1950) and Gough (1953) suggest that œdema fluid forms an excellent culture medium for bacteria, as well as mechanically dispersing infection and delaying the appearance of phagocytes. Blood acts similarly. (ii) Secretions stagnate because the patient cannot evacuate them. (iii) The patient is often impoverished by multiple injuries. (iv) A tracheostomy tube and bronchial aspirations introduce infection into the bronchial tree. Obstruction of larger bronchi is the chief cause of absorption collapse of a segment, a lobe or a lung after injuries of the chest.

II. Diffusion Failure

The chief cause of defective diffusion of gas across the alveolo-capillary membrane is traumatic pneumonopathy, together with its infective and obstructive complications. Occlusion of bronchi and alveoli by blood, œdema fluid and bronchial secretions, and destruction of lung tissue by the injury reduce the effective area of the alveolo-capillary membrane, while interstitial œdema of the lung increases the diffusion distance. Serious impairment of diffusion of oxygen may arise, but that of carbon dioxide is so rapid that it is rarely affected. Intracapillary hindrance to diffusion of oxygen may also increase after injury because of hæmorrhage. This may reduce the pulmonary capillary blood volume and also cause hæmodilution, with lowering of the hæmatocrit reading, so decreasing the amount of hæmoglobin available to oxygen. Impaired diffusion requires oxygen-enriched air in its treatment, but care must be taken to correct associated ventilation failure causing hypercarbia.

III. Gas-blood Distribution Failure

Inadequate ventilation of well-perfused alveoli, causing hypoxæmia, may arise acutely after crush injuries of the chest and upper abdomen in consequence of infra-carinal airway obstruction by any of the mechanisms already described, hæmorrhagic or pneumonic consolidation of the lungs, or pulmonary tamponade. After a relatively short time, e.g. twelve to twenty-four hours, blood tends to be diverted from the underventilated alveoli by constriction of the small pulmonary arteries so that the defect tends to be self-correcting. Inadequate perfusion of well-ventilated alveoli increases the dead space effect to cause an overall defect of alveolar ventilation, unless total ventilation is proportionately increased.

Summary

Ventilation, diffusion and distribution of gas and blood to the alveoli may all be seriously impaired by closed crush injuries of the chest and upper abdomen, and so lead to fatal progressive respiratory failure. Any embarrassment of respiration, either central or peripheral, must be corrected immediately. A classification of respiratory failure following injury is given, and the condition called traumatic pneumonopathy is defined.

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A patient admitted with a severe chest injury is suffering from a lethal triad: bleeding, drowning and suffocation; each of these factors increases the effect of the others, so all must be treated promptly if the patient is to be given the best chance of survival.

When the injury is limited to the chest it is easy to overlook the effect of bleeding. This is well illustrated by a young man who was admitted with a crush injury, pale, dyspnœic and with a high diastolic blood pressure. Physical examination suggested he had fractures of his lower ribs on the left side and a pneumothorax. X-ray confirmed the diagnoses, but his breathlessness persisted after the pneumothorax was aspirated. Further examination revealed a swelling in the left groin, which appeared to be a hæmatoma

from a fractured pelvis. Transfusion of three bottles of blood relieved his breathlessness.

If the injury to the chest is itself sufficiently severe to cause abnormal movement, the patient is likely to have lost a bottle of blood into the muscles, so that this can be regarded as the minimum necessary transfusion in such patients.

Drowning is due to a mixture of secretions and blood in the bronchial tree, which are best removed by direct suction. Suffocation, or mechanical interference with respiration, is caused either by fracture of the chest wall interfering with the respiratory movement or by blood or air in the pleural cavity preventing expansion of the lung. These two factors have an obvious direct effect on each other, both greatly increasing the work the patient has to do in order to breathe; this work, itself, requires an increase in cardiac output which the patient with a diminished blood volume is unable to maintain. It seems logical, therefore, to treat the drowning and suffocation together by intubating the patient, sucking out the bronchial tree, and relieving the patient of the work of breathing altogether by artificial respiration. This produces dramatic improvement in the patient's condition and enables further treatment to be carried out in a more leisurely fashion.

In patients admitted *in extremis* it would seem best to intubate, artificially respire, and transfuse them even before the chest is X-rayed. Once this has been done further measures for the removal of blood and air from the chest and stabilization of the chest wall can be undertaken.

Mr Ivor Lewis (*St Asaph, Flintshire*)

Non-penetrating Injuries of the Abdomen

It may well be held that the classification of abdominal injuries into penetrating and non-penetrating is of more interest to the writer of textbooks than to the surgeon, based as it is on an irrelevant feature – a wound of the parietes. However, the presence of a wound may be of some help in indicating the viscera likely to be damaged and in most cases will in itself cause urgent surgical aid to be sought. The absence of a wound of the parietes means that only the development of symptoms of visceral injury will bring the case under the surgeon's attention. But although there is little inherent value in this classification it so happens that it has acquired a kind of extrinsic utility from the fact that over half the non-penetrating injuries of the abdomen to-day have other associated injuries – of the limbs, the thorax, or the spine, and a good number of the patients are unconscious from a head injury. By contrast a penetrating abdominal injury is usually single and circumscribed. No one in peacetime can have anything like the experience of the war surgeons in abdominal injuries, approach their skill in differential diagnosis, or their brilliant results under difficult conditions. Nevertheless, I am going to advocate lines of management for civilian cases which differ in some important respects from the tenets laid down with such clarity by surgeons like Ogilvie and Rob, remembering that they dealt with war injuries, treated under war conditions, and mostly penetrating.

The patient with an abdominal injury complains of abdominal pain. He is shocked, he may be vomiting, and the abdomen is tender and rigid. Rigidity is so important a sign that we should never use the meaningless and non-committal term of 'guarding'. If the symptoms persist he must be regarded as a case of ruptured viscus. It then becomes a question not of whether to operate but how soon to operate. The question of the viscus ruptured is of less importance. In non-penetrating injuries, where there is no precise indication of the route of the violence, the diagnosis of the viscus injured may be right in perhaps 2 cases out of 3, but it is not possible to say that some other viscus is not injured also. Thus the only sensible decision, whenever it seems likely that a viscus is ruptured, is to look and see, as soon as the patient can be made fit enough. There is one exception to this simple policy, rupture of the kidney, in which the management should be expectant. The late Ruscoe Clarke advocated laparotomy 'on the merest suspicion', but that is probably going too far. In 12 out of his 83 cases no abnormality was found. But if we are to reduce our mortality in these injuries to respectable proportions the price we shall have to pay will be a fair number of negative explorations.

Diagnostic points: The most important measure is the watching of the patient, with careful pulse and blood pressure records, every quarter of an hour, for just long enough for the diagnosis of intra-abdominal injury to be made and thereafter to gauge the effect of morphia and of transfusion till the patient is ready for operation. But the blood pressure and even the pulse-rate may be normal. Referred pain is of the greatest value, especially the pain in the supraspinous fossa or summit of the shoulder in ruptured spleen or liver or any other injury impinging on the diaphragm. It must always be asked for. The patient will not volunteer the remark as the overwhelming pain is in the abdomen itself. There may be referred rigidity in chest injuries. There is no certain way to rule out an abdominal injury as well, except by the development of events, or in certain cases by making a small suprapubic incision under local anæsthesia.

The bowel sounds: It may be taken as axiomatic that established peritonitis abolishes peristaltic sounds. Thus their absence, confirmed by listening for two or three minutes on repeated occasions, is diagnostic of peritonitis. But peristaltic sounds may persist, though faintly perhaps, with peritoneal hæmorrhage and even with escape of urine from a ruptured bladder. 'Shifting dullness' is unkind to the patient and useless to the surgeon.

Two X-ray views may be of the greatest help – of the chest, to exclude pneumothorax or other lung injury, and an upright of the abdomen to show gas under the diaphragm and distribution of gas in the stomach or gut.

Finally, two rubber tubes can be used with great advantage: a stomach tube and a urethral catheter, which can be passed on the operating table so as to have an empty stomach and bladder before operation and to verify that these organs are uninjured.

Pre-operative preparation: An intravenous drip will be set up, morphia given and plasma transfusion started. In some cases two or three hours can be spent in improving the patient's condition and in cross-matching blood. If, in spite of generous resuscitative measures, his condition fails to improve then it is due to sharp continuing internal hæmorrhage and the operation should not be further delayed.

The laparotomy: A mid-line or paramedian incision is probably best on account of its easy extensibility. Initially it should be just large enough to admit the hand easily, with its upper end reaching only 2 in. above the umbilicus. Then, according to what is found, the upper end is extended upwards vertically, or obliquely, across the costal margin if liver or diaphram is injured. There must be no hesitation about this extension into the thorax where called for.

An obvious gross lesion will be dealt with at once. The organs should be quickly and systematically inspected, starting at the cæcum and working upwards, placing the small gut into a gauze bag or warm gauze as it is delivered. With the small gut out of the way, one inspects the colon, duodenum, stomach, liver, spleen, pancreas and the diaphragm. A note is also made of any exudate, bloody or watery, around the kidneys or ureters. The surgeon should aim at completing the operation within the hour, although the careful surgeon should not be forced to violate his nature. As for the indecisive dawdler he might bethink himself of an occupation in some quieter backwater than the surgery of ruptured viscera.

In this summary there is no room for discussion of the individual viscera except for a few comments on the liver.

Liver: It has long been taught that in rupture of the liver alone, one should be obstinately conservative. It is not reasonable to make any such rule in the case of the blunt diffuse violence of civilian surgery. First, there is a good chance of some other viscus being ruptured as well. Secondly, it may not be the liver at all, but as the symptoms and signs indicate a laparotomy we shall draw the dividend on the 'look and see' policy. Thirdly, bile peritonitis, even if the hæmorrhage has ceased, may kill the patient. The average surgeon is unlikely to see more than a dozen or so ruptured livers in a surgical lifetime and it will therefore not profit him to try and have a different set of rules for the torn liver.

What should one do with the tears? With porta hepatis compression and good suction any large vessels and bile ducts in the depth of the liver should be sutured by criss-cross transfixion with an atraumatic suture of catgut. Much and varied advice has been given on how to suture the torn liver. Actually all that is needed is a large curved eyeless needle with No. 2 catgut and with some deeper tears a still larger curved needle with soft double catgut tied at the end. The sutures can be passed quite deeply and tied individually or in short lengths. With a little practice and reasonable finger sense these sutures can be tied just right if the assistant holds the liver together. Those of us who make a practice of suturing the gall-bladder fossa after cholecystectomy will be adept at this. The inaccessible tears on the posterior surface may have to be packed; but with a really free incision across the costal margin and into the chest most of them can be sutured.

Traumatic rupture of diseased organs: Finally, this interesting possibility merits a word. If one is surprised that an abdominal injury should have been caused by the particular accident described then one should think of a diseased organ having been ruptured. In the tropics large spleens are often ruptured by a slight impact. I have known a boy slip while mounting his bicycle and rupture a hydronephrosis and a woman rupture an ovarian cyst against the corner of an armchair.

Mr Ashton Miller (*Bristol*)

Closed Injuries of Kidney, Bladder and Posterior Urethra

These two injuries commonly occur as isolated results of trauma uncomplicated by injuries elsewhere. They are predominantly injuries of young people.

The Kidney

The mechanism of injury is that a blow in the loin rotates the twelfth rib forwards which squeezes the kidney between itself and the sides of the

bodies of the lumbar vertebræ. One-quarter of our patients sustained their injuries playing football and one-quarter in traffic accidents. All degrees of injury have been seen ranging from a minor contusion which produces hæmaturia to a severe injury involving shock, hæmaturia and hæmorrhage into the perinephric tissues producing a mass in the loin. One-third of our cases came into the severe category and two-thirds were mild.

I am indebted to my colleague, Mr Norman Slade, for figures from his paper on the late results of renal trauma which is awaiting publication in the *British Journal of Surgery*. He reviewed 59 cases and found that only in 12 of these 59 were there associated injuries elsewhere, and only in 4 out of the 59 was the injury to the kidney not the main injury. Of these 4, 3 had multiple injuries resulting in rapid death, and the fourth, in addition to a ruptured kidney, had a ruptured spleen.

The diagnosis is usually made by the history of trauma to the kidney region and the occurrence of hæmaturia shortly afterwards. A mass is sometimes felt in the loin; fracture of overlying ribs is unusual. Bowel sounds are usually present in the abdomen, though ileus may occur some hours later.

Most people are agreed on the management of these cases: bed rest, sedation with morphine and frequent, possibly half-hourly, observation of the pulse-rate and blood pressure. Transfusion of blood is rarely necessary and we have found that keeping urine specimens to observe the increase or decrease of the hæmaturia or alterations of colour of the blood in the urine is of no value. The degree of hæmaturia and the length of time that it continues are variable and bear no relation to the severity of the injury. Intravenous urography is very useful and should be performed as soon as the patient is fit enough to be moved from his bed to the X-ray department; it should not be done with a portable X-ray machine. It tells us three things; first, the severity of the injury to the affected kidney; secondly, the presence and adequacy of the other kidney; and thirdly, the presence of any pre-existing renal abnormality. We never do a retrograde pyelogram because we feel it may introduce infection and is unnecessary if an intravenous pyelogram can be done. We have found antibiotic cover useful. No less than 7 out of 59 cases spontaneously developed an infection in the urinary tract following injury.

The only indication for surgery is hæmorrhage severe enough to endanger life. This is usually of the reactionary type and hence the need for pulse and blood charts. If surgery is decided upon, a blood drip should be set up and the kidney should be explored in the kidney position on the operating table. The first part of the operation consists of opening the peritoneal cavity to exclude injury there and the second of trying to preserve the injured kidney, but in most cases it will be found that exploration is equivalent to nephrectomy. Five out of our 59 cases were taken to the operating theatre. Three of these had nephrectomy, 1 had partial nephrectomy (the injured kidney being solitary) and 1 had splenectomy performed, a ruptured spleen being removed and the associated ruptured kidney being left untouched.

The long-term results are excellent, in the great majority there being no untoward sequel whatever. In these 55 cases followed from three to eight years there is no single case of hypertension. It is notable that in this series there is a high incidence of previously abnormal kidneys, of which hydronephrotic kidneys predominate.

Ruptured Bladder and Posterior Urethra

Both these injuries are most commonly complications of a fractured pelvis and we think that they are not distinguishable from one another without operation or exploration, so that for practical purposes we can regard them as the same injury. Diagnosis is made by knowing that the patient has a fractured pelvis and knowing that a ruptured urethra or a ruptured bladder is a possible complication of the fractured pelvis. We then wait and see what happens. We believe that the diagnosis of injury to the urinary tract can be made without urethral instrumentation by catheter and that catheterization should be avoided. Knowing that the patient has a fractured pelvis, we keep him under observation in bed and one of several things must happen. Either he will pass urine spontaneously and if this urine is clear and contains no blood we have no further worries because this indicates that the urinary tract is intact and his further treatment is an orthopædic rather than a urological problem. Secondly, he may be unable to pass urine and may become very distressed with a palpable distended bladder. This means that something has to be done and we know that he must be taken to the theatre. Thirdly, he may pass some blood from the external urinary meatus without being able to pass urine. This again indicates an injury to the urethra and surgery is necessary. Fourthly, he may develop a mass in the suprapubic region which may either be a distended bladder or extravasation of urine combined with hæmatoma around the bladder and in the extraperitoneal space within the pelvis. Fifthly, rectal examination may disclose the prostate displaced upwards and replaced by a hæmatoma. Incidentally, an early rectal examination of every patient with a fractured pelvis is essential, not only to elicit this physical sign in the region of the prostate if it is present, but also to feel if the rectum is intact. I had one patient in whom on rectal examination I

came up against a sharp fragment of pubic ramus projecting into the cavity of the rectum, necessitating a colostomy immediately.

When the patient is taken to the theatre, a suprapubic cystostomy is performed without instrumentation of the urethra. If there is any doubt about a coincident injury of intraperitoneal organs, the peritoneum can be opened at the beginning of this operation and intra-abdominal exploration performed. Otherwise, the bladder is opened and a suprapubic tube inserted. If by any chance that part of the bladder wall covered by peritoneum is involved, then it is better to suture this, but if the anterior part of the bladder wall is involved it is usually in the form of a small split which will heal spontaneously once the bladder is empty and drained. In those rare cases where the bladder and prostate are apparently completely separated from the triangular ligament, the same treatment should be performed and no attempt should be made to draw the bladder down by passing, for example, a Foley catheter *per urethram*. It will be found that in the two to three weeks after injury, the bladder will be drawn back to a great extent to its normal position and union of the ruptured urethral ends can be achieved in the third week without much difficulty. It is also recommended that some attempt should be made to reduce the bony deformity resulting from the fracture of the pelvis. Much of the difficulty of instrumentation after these injuries is due to this bony deformity and not so much to trauma to the urethral mucosa. Reduction of the fracture is always extremely difficult and may need much force, but anything that can be done to reduce deformity influences greatly the success of after-treatment of the urethra.

This policy of endeavouring to make the diagnosis without catheterization of the urethra has been advocated for the past seven years by my colleague, Mr John Mitchell, and all cases which have been admitted to our hospitals have been treated in this way with extremely satisfactory results. Catheterization is not only unnecessary, but dangerous, because it may cause an infection at the site of the rupture of the urethra and may unwittingly increase the damage in a partial rupture of the posterior urethra. Extravasation of urine is harmless if it is not infected and if it is eventually drained. The first duty of the surgeon when dealing with these injuries is to save life. The definitive treatment of the ruptured urethra can more satisfactorily be left until the third week after the injury when the hæmatoma is absorbed and the affected tissues are restored much more to normal, so that suturing can be done more easily and instrumentation can be done with impunity. All the lethal complications of a fractured pelvis are due to infection and if this can be avoided we have gone a long way towards making sure that the patient does not die from his injury. This injury is very different from rupture of the kidney which can usually be described almost as trivial, but rupture of the bladder or posterior urethra is never trivial – it is always potentially dangerous.

Mr H M Stevenson (*Belfast*)

The two cases described below illustrate some interesting points in the method of production and the treatment of severe and widespread surgical emphysema associated with fractured rib, and the associated lesion in the lung. The first of these patients died, and the lesson we learnt from this case enabled us to operate successfully on the second patient.

Case 1 A painter, aged 53, was admitted to hospital after being knocked down by a car which struck him on the right side. *On admission* he was found to be recovering rapidly from concussion and to be complaining of pain in the right side where X-rays showed that he had fractured his ribs from the 2nd to the 10th inclusive. The right lung field was dense but the lung was not collapsed; neither (and this is of importance) was there any pneumothorax. Slight surgical emphysema over his right chest was noted at this time but the thoracic cage was normal in contour and there was no falling in of the ribs.

He was treated conservatively, propped up in bed, and at no time during the first few days after his admission was there any serious respiratory distress. During the forty-eight hours after admission the surgical emphysema increased considerably, extending eventually from the top of his head to his scrotum and into his arms and hands. Radiographs at this time were not satisfactory because of the surgical emphysema. They showed progressive falling in of the upper right chest wall. A small amount of fluid appeared to be accumulating in the right hemithorax. The surgical emphysema progressed.

On the sixth day after the accident, his general condition deteriorated rapidly, respirations became laboured, the pulse rate rose steeply, and there was evidence of much retained secretion from his tracheobronchial tree. For the first time, he was unable to cough satisfactorily. In spite of tracheostomy he died.

At post-mortem: (1) The positions of the fractures were confirmed. (2) The 4th rib alone had pierced the parietal pleura and a spicule of it had impaled the lung holding it into the parietal laceration. (3) There were no pleural adhesions to account for the absence of the pneumothorax. (4) Lying deep to the superficial tear in the surface of the lung produced by the spicule of bone there was a liquefying hæmatoma measuring about $2 \times 1\frac{1}{2}$ in. (5) Both lungs were heavily infiltrated with a bloody effusion which involved the whole of the right lung and the lower lobe on the left side. (6) There was no tear in the tracheobronchial tree.

We think this man's death was due to the effects of the anoxæmia produced by the widespread bleeding into the lung. His gross surgical emphy-

sema rather distracted us from the underlying anoxæmia. We think, in this case, that the surgical emphysema neither caused much obstruction to his airway nor contributed materially to his anoxæmia. This has also happened in another case (not discussed here).

After the post-mortem we felt that had we done a thoracotomy and unhitched the impaled lung we would have allowed the damaged lung to collapse and probably saved a good deal of the subsequent intrapulmonary bleeding. Also we would have arrested the surgical emphysema.

Case 2 A man aged 40 was admitted to hospital after receiving an accidental blow, at work, by a beam falling across the upper left chest. *On admission* he complained of severe pain in the upper left chest and there was marked tenderness over the left scapula with slight surgical emphysema in this region.

X-rays showed a fracture of the left scapula and possibly a fracture of the neck of the 2nd rib. There was no pneumothorax. He, too, was treated conservatively at first but the surgical emphysema spread to involve the chest wall and the head and neck. Five days later a radiograph showed the same progressive clouding of the lung. His condition was deteriorating a little and the surgical emphysema was further increasing. We remembered the previous case in which the essential pathological lesion appeared to be the capture of the lung in the fracture line of the rib. We decided to explore the chest. A moderate amount of heavily blood-stained fluid was found in the pleural cavity. At the apex of the upper lobe there were a number of small bullæ, one of which was leaking air. There were no pleural adhesions. The posterior end of the 2nd rib was fractured and the small spicule of bone had penetrated the parietal pleura and, we presumed, had produced the small tear in the lung from which the air was leaking. The leak was closed, the bony fragment removed, and the lung re-expanded satisfactorily. The post-operative course was uneventful.

The features of importance in these cases seemed to us to be the following:

(1) Both patients had fractured ribs, in one case multiple and in the other, single. But in each case only one rib had perforated the parietal pleura and it produced a minor laceration of the lung adjacent to it.
(2) The rib, in snapping open and then springing back again, had captured a small piece of lung and this had two effects: (*a*) the air could escape into the parietal tissues, and (*b*) a pneumothorax was prevented from forming. Therefore the lung did not collapse.
(3) Progressive surgical emphysema of the thoracic wall occurred over several days and reached alarming and even dangerous proportions.
(4) Thoracotomy, with unhitching of the lung and establishment of under-water drainage, seemed to cure the second patient.

It is possible that this phenomenon of crack capture of the lung by a fractured rib is not infrequently the cause of surgical emphysema which, because it spreads along the main axillary vessels and up into the neck, might be thought of as coming only from the mediastinum.

Mr Derek Richards (*Newport, Mon.*) emphasized that from his experience at the Royal Gwent Hospital, Newport, often patients with non-penetrating injuries of the chest or abdomen presented with other injuries, such as of the limbs and face, which were more obtrusive than the visceral injuries, and that this might therefore lead to the vital injuries being overlooked. He also urged that the question of who was primarily responsible for a patient with multiple injuries should always be clear, since a patient cannot be treated by a committee.

Mr W R Probert (*Penarth, Glam.*) described a case to show that the early use of intermittent positive pressure respiration after chest injury did not give unlimited time to review the clinical situation.

He also stressed the frequency of serious and often unsuspected injuries of the heart and great vessels after closed chest injury. Hæmatoma of the inter-ventricular septum is important both as a possible cause of heart block and, through later necrosis, of traumatic ventricular septal defect. Though most injuries of this type cause immediate death, there are intermediate degrees of injury in which operative treatment may help.

Mr R V Cooke (*Bristol*) referred to lessons learned from a survey he had made of abdominal injuries admitted to the Bristol Royal Hospital over a period of twenty years. Resuscitation was persisted with too long, and operative treatment undertaken too late. Resuscitation can be started at once, and if need be continued during and after laparotomy. In this series, as in others, there was a tendency to operate only when the indications were irrefutable, instead of exploring when the signs, though meagre, were sufficient to arouse suspicion of an intra-abdominal injury. Another lesson was the frequency of multiple injuries. It was easy to remove the ruptured spleen, but miss the rent in the liver, or a mesenteric tear depriving gut of its blood supply. Simple packing of a liver injury had proved to be uniformly unsuccessful in this series.

Prevention is always better than cure, however skilful or heroic. There was much to be said for revising motor car design, and the speaker was surprised that no one had mentioned the modern safety belt. Our American colleagues had proved its life-saving value.

Section of Neurology

President W H McMenemey MD FRCP

Meeting January 5 1961

Discussion on Steroid Therapy in Neurological Disease

Professor I E Bush (*Birmingham*)

Basic Considerations in the Use of Anti-inflammatory Steroids in Neurological Diseases

The treatment of any disease with anti-inflammatory steroids is fraught with complications that can only be understood in terms of the normal physiology of the adrenal cortex and the metabolism of its products of secretion, or of the particular steroid that is used. Much recent work on these topics is still not dealt with adequately in the textbooks and yet bears very closely on the problems that clinicians face every day in the treatment of their patients.

The most important question in this field is, 'What tissue or tissues do we affect with cortisone-like steroids when we successfully ameliorate the effects of an inflammatory disease, and what factors govern the concentration of steroid in these tissues that is achieved by our treatment?' It is probably better, however, to consider first the normal behaviour of the human adrenal cortex and how this is affected by our treatment, since in this field lie some of the most important consequences for our patients. It is not yet sufficiently realized that changes in the rate of adrenocortical secretion of cortisol (hydrocortisone) and corticosterone can be extremely rapid (Bush 1953) and that its regulation by the secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland is governed in turn by structures in the central nervous system which are also capable of very rapid responses (Harris 1955, Gray & Munson 1951, Bush *et al.* 1953). Thus, Gray & Munson showed that the fall in the ascorbic acid concentration of the rat's adrenal gland produced by an intravenous injection of histamine was prevented completely by an intravenous injection of adrenocortical extract 5 seconds before the histamine; diminished by giving the adrenocortical extract simultaneously with the histamine; but quite unaffected by giving the adrenocortical extract 5 seconds after the histamine. Bush *et al.* (1953) showed that, in the dog, infusions of cold saline into the external carotid artery caused an increase in adrenocortical secretion within the first two minutes, while a similar infusion of saline at 39°C caused a fall in the same time. The same infusions into a peripheral vein produced little or no change. It is probable that on the first day of treatment of a human subject with more than 50 mg of cortisone or 15 mg prednisolone, the secretion rate of cortisol drops to 10% or less of its normal value. This adrenal 'suppression' is produced through the normal mechanisms in the central nervous system and anterior pituitary gland; while it is usual to emphasize the atrophy of the adrenal cortex that follows prolonged treatment with cortisone-like steroids, it should be remembered that 'atrophy' of the hypothalamus-hypophyseal regulatory system, structural or functional, or both, must also occur to some extent. It is also known that the adrenal of the rat loses its ability to respond quickly to ACTH within one week of hypophysectomy, long before its structural atrophy is complete (Bush & Stack-Dunne 1951).

Two other features of normal adrenocortical secretion in man need emphasizing since they give rise to unnecessary puzzlement in clinical practice. The first is that emotional factors appear to be far more potent stimulators of the human adrenal cortex than those physical factors commonly called 'stresses'. Thus, cold and severe physical exercise do not seem to cause more than trivial increases in adrenocortical secretion rate unless accompanied by psychological 'stress'; psychological strain can cause very large increases in adrenocortical secretion rate and/or of the plasma concentration of cortisol in the absence of any physical exercise (Hill *et al.* 1956). The role of emotional factors has recently been investigated very thoroughly both in human subjects and monkeys by Mason (1959). Bush & Lovell (1954) found that excretion rates of the metabolites of cortisol were raised to levels found otherwise only in severe Cushing's syndrome by the anxieties of

awaiting and undergoing an interview for a new post, or by those of the *viva voce* examination in the London MD. Bayliss & Steinbeck (1954) found equally large increases in the plasma concentration of cortisol in subjects about to give papers before a learned society.

The second feature, which is probably partly dependent upon the first, is the great variability of adrenocortical function both between individuals at any one time of investigation, and between different times in the life of one individual (Forsham *et al.* 1955). The normal range of excretion of the metabolites of cortisol in unselected subjects is large (Bush & Willoughby 1957) and as yet we do not know what factors cause this variability; emotional factors could cause effects large enough to account for all of it but there is no evidence yet to exclude other factors, although variations in the metabolic disposal of cortisol are usually not large enough to account for more than a small part (Hill *et al.* 1956, Bush & Willoughby 1957). The range of the normal values for the concentration of cortisol in the plasma of unselected subjects is also large (Nelson & Samuels 1952). The profound influence of œstrogens upon this value is probably the basis of the very large increases found in the last trimester of pregnancy (Bayliss *et al.* 1955, Mills & Bartter 1959). Another source of variability is the influence of thyroid hormones upon the rate of removal of cortisol from the blood (Peterson 1958).

In the face of this variability, investigators should not be surprised to find that the effects of steroid therapy also appear to vary widely. It is safer to assume that adrenocortical function will be seriously inadequate in the patient who has had a course of cortisone-like steroids for more than a week or two, than to take the not infrequent exceptions to this rule too optimistically. On the other hand, it is probable that the secretion of aldosterone by the zona glomerulosa of the adrenal is under the control of a system different from that responsible for the regulation of the secretion of cortisol and corticosterone (Ayres *et al.* 1956, Mills *et al.* 1958, Farell *et al.* 1956) although it is partly, or at least indirectly, affected by ACTH.

Another important feature of normal adrenocortical physiology that has only recently become established is the role of the 'binding' of cortisol and some other cortisone-like steroids by an apparently specific plasma protein called 'transcortin' (Daughaday 1956, 1958, Bush 1957, Slaunwhite & Sandberg 1959, Mills & Bartter 1959). At plasma concentrations in the normal range (5–20 μg/100 ml), this material associates with cortisol at physiological temperatures so that only about one-tenth of the total plasma cortisol is freely diffusible across a dialysis membrane. The normal concentration of cortisol in human cerebrospinal fluid, determined approximately by Baron & Abelson (1954) is exactly that predicted from the assumption that this relation holds for the blood/brain barrier (Bush 1957). The link with this carrier protein, however, is broken by ordinary methods of extracting cortisol from plasma so that the total freely extractable cortisol (i.e. 'unconjugated' in the usual sense) is usually much greater than the probable concentration of this steroid in tissue fluid. This supposition is confirmed by the findings of Sandberg *et al.* (1954) and of Cope *et al.* (1955) on serous exudates and other fluids in man although the latter authors' results were probably complicated in some cases by an unknown degree of damage to the blood vessels from which the exudates had been formed (Sandberg *et al.* 1954). The physiological importance of this phenomenon has been emphasized by the findings of Mills & Bartter (1959) that the large increase in the concentration of freely extractable cortisol in the plasma of women in late pregnancy is almost entirely in the non-diffusible fraction of cortisol and is paralleled by a great increase in the concentration of transcortin, all of which can be mimicked in non-pregnant women, or in men, by a relatively short course of treatment with œstrogen. These workers showed that the 'bound' cortisol was probably unavailable to the tissues and physiologically 'inactive' as suggested earlier (Bush 1957).

The anti-inflammatory action of cortisone-like steroids is almost certainly due to a direct effect upon the inflamed tissues and the tissue elements involved in the response to the causative agent, and not wholly to an indirect consequence of the effects of these steroids upon the general metabolism of the body. It is not yet clear, however, whether these direct effects upon inflammatory tissue-elements are themselves the same as the metabolic effects upon the liver, and probably other tissues, which produce the well-known metabolic alterations found in Cushing's syndrome, or whether they represent a totally different type of effect. The analysis of the anti-inflammatory effects of cortisone-like steroids will only be completed when we know more about inflammation itself. Thus, the majority of assays employed to assess the anti-inflammatory potency of cortisone-like steroids involve a granulomatous reaction to a solid foreign body, or an exudate provoked by a liquid irritant. These reactions almost certainly bear little or no resemblance to the majority of inflammatory diseases which can be treated with these steroids. The complications of this field are well shown by the fact that subcutaneous exudates due to turpentine or croton oil are greatly diminished by the administration of cortisone-like steroids, while intrapleural exu-

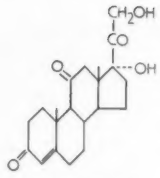

Fig 1A, *cortisone*

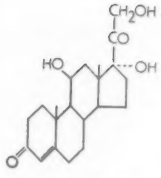

Fig 1B, *cortisol*

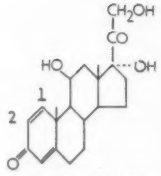

Fig 1C, *1, 2-double bond (prednisolone)*

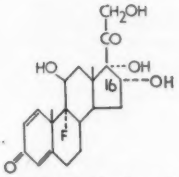

Fig 1D, *16α-hydroxyl group (triamcinolone)*

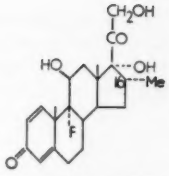

Fig 1E, *16α-methyl group (dexamethasone)*

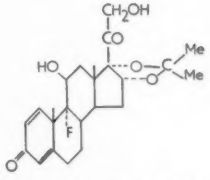

Fig 1F, *16α, 17α-ketonide group (triamcinolone acetonide)*

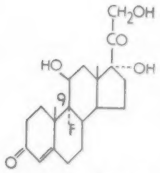

Fig 1G, *9α-fluorine atom (9α-fluorohydrocortisone)*

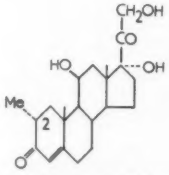

Fig 1H, *2α-methyl group (2α-methylhydrocortisone)*

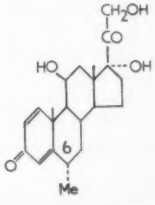

Fig 1I, *6α-methyl group (6α-methylprednisolone)*

dates are quite unaffected by enormous doses of cortisol in rats (Spector & Willoughby 1959). This is probably one of the reasons why the very high activity of certain analogues of cortisol in the cotton-wool granuloma assay is not usually matched by their activity in controlling collagen diseases in man.

Most of the analogues of cortisol owe their enhanced activity largely to the presence of substituents or modifications of structure which decrease the rate at which they are inactivated by the liver. In the 9α-fluorosteroids, however, another factor almost certainly exists. The fluorine atom increases the strength of any hydrogen bonds formed with the proton of the 11β-hydroxyl group (Fried 1955, 1957) and the redox potential difference of the reaction

11 β-hydroxyl group ⟶ 11-ketone group

is greatly increased in the direction of increased stability of the hydroxyl group. This results in an almost complete prevention of the oxidation of the hydroxyl group upon which activity depends (Bush & Mahesh 1958, Bush 1961). In the non-fluorinated analogues of cortisol, the 11β-hydroxyl group is oxidized to a considerable extent to the 11-ketone group which is almost certainly inactive at the receptor for these hormones; this represents a wastage reaction of the active hormone because reduction to the active form can only occur to any great extent in the liver, a process which is attended by considerable losses via the normal inactivating reactions which are also carried out by the liver (Bush 1956, Bush & Mahesh 1959, Bush 1961). The effect of the 9α-fluorine atom in 11-oxygenated steroids might be described therefore as twofold: it increases the affinity of the hormone for its receptors, and it stabilizes the hormone in its active (reduced) form.

Most of the analogues of cortisol show only one important type of difference from cortisone and cortisol themselves in their spectrum of biological actions. This is the reduction of salt-retaining activity that is achieved by the following modifications (Fig 1): (*a*) Placing an extra double bond between C–1 and C–2; (*b*) Introducing a 16α-hydroxyl group; (*c*) introducing a 16α-methyl group; (*d*) introducing any large 16α-substituent (e.g. the 16α, 17α-ketonide radical), and the increase in such activity caused by (*e*) introducing a 9α-halogen atom, especially fluorine; (*f*) introducing a 2α-methyl group; (see Fried & Borman 1958, for references).

A few of the analogues produce bizarre effects in man which are sufficiently different from those of other analogues to be of clinical significance. Thus, triamcinolone appears to cause a high incidence of muscle wasting and degenerative changes in the joints, and often disturbances of sleep, appetite and emotion. A very useful review of most of the important structural modifications found in analogues of cortisone and cortisol is given by Fried & Borman (1958). These authors also give a full discussion of the effects of these modifications on biological activity in animal tests. At present the most useful analogue in my opinion is prednisolone (Fig 1) although it is only four to five times as active as cortisol. It lacks any serious salt-retaining activity and is no worse and no better than cortisone and cortisol in other side-effects. The only advantage of the more potent analogues such as triamcinolone or dexamethasone (Fig 1) is in tests of adrenal function or steroid metabolism; the dose capable of suppress-

ing endogenous adrenocortical secretion is so small that the excretion of the metabolites of the administered steroid can be neglected when carrying out estimations of other urinary steroids.

These considerations may require some modification in the case of diseases of the nervous system. Thus, it is quite possible that certain analogues will be found to penetrate nervous tissue and reach a site of inflammation better than others. This might confer marginal, or even considerable, advantages over other steroids in terms of the largest dose that can be used for a given severity of undesirable side-effects. But it is unlikely that such advantages will be large since it is highly probable that the damaged capillaries of an inflamed area in any part of the body will offer little resistance to the passage of steroids.

What type of condition is likely to respond well to treatment with cortisone-like steroids? It is probably safe to say that most of the conditions that show an undoubtedly beneficial response involve a hypersensitivity reaction of the delayed type. But fibromatous and granulomatous reactions, which are probably not of this type, are also inhibited by these steroids and in some diseases it may be of benefit to inhibit such reactions. In diseases of unknown ætiology it is worth remembering that resistance to infections of all types is reduced by these steroids when the usual 'therapeutic' doses are given. On the other hand, fulminating diseases with shock-like states may be benefited by these steroids in a manner which is little understood; the position is, however, controversial. Certain inflammatory diseases in man, which are undoubtedly inhibited by cortisone-like steroids, have not yet been surely classed as belonging to any particular type of allergy, e.g. ulcerative colitis, and certain skin diseases. This fact, coupled with the knowledge that some reactions to foreign bodies and irritants, and the Schwarzman reaction, under certain conditions (see Thomas 1953), are also inhibited by these steroids, should make it clear that many types of inflammation may be responsive to treatment with them. The fact that a particular disease of unknown ætiology does respond favourably should not be used as an argument in favour of its belonging to the group of delayed allergies, without supporting evidence.

One of the most important questions worrying the clinician is the suppression of adrenocortical function after therapy with cortisone-like steroids. It is difficult to believe some of the more extreme views on this matter; for instance, that a few weeks' treatment may lead to fatal adrenal insufficiency during a surgical operation several years later. But patients should be very carefully weaned from cortisone-like steroids and all patients who have received more than the equivalent of 30 mg cortisone daily for more than two weeks should carry a card giving details of their treatment. Their adrenocortical function should be assessed after weaning at least by the measurement of their urinary steroid excretion or their plasma cortisol concentration before and after ACTH, and preferably in response to pyrogen, SU-4885 (Liddle 1961), or some standard 'stress' causing a natural stimulation of the secretion of ACTH. Some indication of their performance under such tests should be entered on their card before they leave the care of the physician who administered their treatment. This standard cannot be met in most medical centres in this country but every effort should be made to achieve it if tragedies are to be avoided. In view of the variable results obtained by intermittent administration of ACTH during a course of therapy with cortisone-like steroids, there is at present no substitute for some sort of test of adrenocortical function before patients can be considered good risks in the event of infection, trauma, or surgery.

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Clinical Applications of Steroid Therapy in Neurology

Interest in the neurological application of steroid therapy dates from shortly after the introduction of corticotrophin (ACTH) and the early demonstration of its inconstant but sometimes apparently dramatic effect in suppressing the neurological as well as the general manifestations of polyarteritis nodosa.

Rich's clinicopathological and experimental studies of this disease opened a new door (Rich 1942, 1947). Neurological disturbances involving every level of the neuraxis are an integral feature of polyarteritis nodosa, and furthermore they often take the form of well-defined syndromes (mononeuritis multiplex, symmetrical mixed polyneuritis, polymyositis, focal cerebral deficit, pseudotumour cerebri, spinal cord and cauda equina lesions) with which we are familiar in other contexts as isolated events of entirely obscure pathogenesis. But Rich's work showed that all these syndromes as they occurred in polyarteritis nodosa had their origins in a disseminated exudative vasculitis, revealed by his collateral studies of serum sickness as an ætiologically nonspecific but pathogenetically characteristic response to a wide variety of initiating antigens, some infective and others merely chemical. The disease furnished striking illustrations both of the part which may be played in the pathogenesis of focal nervous lesions by the humoral influences of general pathology, and of the apparent origin of a group of neurological disorders in allergic lesions of the mesodermal-vascular ground-substance of the nervous system.

This is the context of the present discussion. If the polyneuritic lesions of polyarteritis could sometimes be dramatically suppressed by steroid therapy what other nervous diseases might prove to be similarly accessible? At that time few clinicians in Britain were familiar with the pioneer studies of American experimentalists on the adjuvant-facilitated production of experimental allergic encephalitis by inoculation with brain emulsions, and still fewer with work (Kabat *et al.* 1951, 1952) which demonstrated the inhibition of this reaction by cortisone. Even on clinical and pathological ground, however, it seemed possible that acute disseminated encephalomyelitis (para-infective perivenous demyelinating encephalomyelitis) might furnish a field for steroid treatment. Not only were the lesions of this disorder non-specific, inflammatory, exudative, post-infective and concentrated in the vicinity of blood vessels, but arteritic lesions themselves had been recognized to occur in post-infective encephalitis for more than half a century.

Acute Disseminated Encephalomyelitis and Related Syndromes

It is now nearly ten years since I treated my first case of this kind with ACTH (Miller 1953) and observed an apparently dramatic response. The patient was a 22-year-old medical student who developed a rapidly progressive transverse myelitis with lumbar pain, dysuria and profound weakness of the legs and back, within a few days of an influenzal illness. The administration of ACTH was begun forty-two hours after the onset of neurological symptoms. Subjective improvement began within 90 minutes and complete recovery was rapid and uninterrupted except for one brief phase when the inadequacy of the patient's physiological response was manifest in a rising eosinophil count: increased dosage was again followed by improvement within four hours.

Since then I have treated more than 40 patients with acute para-infective nervous illnesses of encephalomyelitic type, excluding the Guillain-Barré syndromes. On many occasions I have seen an apparent response similar to that described above – restoration of consciousness within twelve hours of administering ACTH to a child stuporous or comatose in the course of measles or chickenpox encephalitis, or unequivocal improvement in spinal function beginning within a few hours of giving ACTH to a patient with a severe and progressive cord lesion. Unfortunately such a response is not invariable, and even now I am uncertain whether these results imply a genuine therapeutic response or whether they are merely coincidental. I can see no practical way of answering this question. A disease of which a population of two million yields less than a dozen examples in a year does not lend itself to the controlled therapeutic trial which alone would solve the problem. Such a trial would need to be conducted nationally in many centres.

However, laboratory evidence lends some support to the view that steroids have a therapeutic as well as a prophylactic value in experimental allergic encephalitis. Gammon & Dilworth (1953) claimed that intensive treatment with corticotrophin exerted a beneficial effect on animals already paralysed, but the doses used were astronomical in relation to the size of the animals. In a recent series of controlled experiments, employing more physiological dosage and as yet unpublished, E J Field and I have demonstrated an unequivocally favourable effect of ACTH on the clinical course of the illness and on residual neurological deficit (spasticity), even when the administration of the drug is delayed until the onset of the encephalitic illness. Since such clinical evidence as is available in relation to the analogous human syndrome points in the same direction (Selling & Meilman 1955) I am now reluctant to withhold

steroid therapy from any case of acute disseminated encephalomyelitis.

I have also had the unusual opportunity of treating two patients with acute neurological symptoms following serum sickness. Both of these patients were doctors. In each the general manifestations of serum sickness were severe, and in both neurological symptoms appeared as the somatic discomforts faded. The first was a classical example of acute and intensely painful shoulder-girdle neuritis accompanied by disappearance of deep reflexes suggesting an incipient polyradiculitis. The second was a case of bilateral retrobulbar neuritis. In both cases recovery began within hours of the administration of cortisone and was complete.

Disseminated Sclerosis

The current vogue of a unitary theory of demyelinating disease (Miller & Schapira 1959) suggested the application of these observations to disseminated sclerosis. Initial small-scale trials such as those of Glaser & Merritt (1952) and of Gibbons and myself (Miller & Gibbons 1953) had been discouraging, but here at least was an opportunity for a more extended and effectively controlled 'double-blind' trial. The first such trial has been completed (Miller *et al.* 1961) and another is still under way.

In the first of these, three groups each of 30 patients with established multiple sclerosis were treated 'blind' with prednisolone, soluble aspirin, and dummy tablets respectively for a period of eighteen months. During this period of observation five acute exacerbations occurred amongst patients receiving dummy tablets, eight in the salicylate and six in the prednisolone group; nor did the prednisolone group show any advantage in the matter of carefully recorded 'disability scores' which measured clinical deterioration. I think these observations dispose of maintenance treatment with prednisolone in this disease.

The second trial concerned patients with acute exacerbations of multiple sclerosis. During the past eight years we have treated a considerable number of such cases without controlling our observations, and we have continued to employ this method empirically in patients who do not fulfil the criteria for inclusion in the trial which we instituted two years ago. If we were guided entirely by clinical impressions in assessing this form of treatment our conclusions would be distinctly unfavourable. The occasional patient who shows continuous clinical deterioration throughout the period of treatment makes a considerable impression, and although in other cases we have several times seen acute symptoms recur within a few hours of withdrawing treatment, I think there is nobody in my department who is really confident about the value of steroid therapy in these acute episodes. However, clinical impression is a fallacious guide and there are occasions when a controlled trial may be as necessary to reveal marginal benefit as to exclude a therapeutic effect. During the last two years we have treated 25 acute exacerbations of disseminated sclerosis which fulfilled the strict criteria laid down for inclusion in the trial. Each patient manifested *assessable new symptoms or signs of less than fourteen days' duration showing no spontaneous improvement*, and the cases were randomly allocated to groups receiving ACTH and saline respectively for fourteen days. The results of treatment have been assessed by an observer who was unaware whether ACTH or saline had been administered. We have found considerable difficulty in classifying our results. In this instance the numerical scoring of disability has proved unsatisfactory, because the recent symptoms represented so variable a proportion of the total disablement, and we have finally had to be satisfied with classifying the apparent response into groups A, B, and C. In group A the rate and completeness of resolution of recent disability were so rapid and so striking that an observer unfamiliar with the natural behaviour of the disease would have postulated an unequivocal therapeutic response. At the other end of the scale, group C comprised those cases with little or no improvement during the fourteen days' treatment. When we came to analyse our results we found that group A included 7 of the 13 cases treated with ACTH, and only 3 of the 12 treated with saline. Group C comprised 4 of the 12 cases treated with saline and only one of the 13 treated with ACTH. These results are apparently statistically significant and seem to indicate a beneficial effect of ACTH in acute episodes of disseminated sclerosis. However, I think we must be cautious in equating biological with apparent statistical significance. I am less concerned that the finding runs counter to clinical impression than that the total number of cases is so small in a disease where the behaviour is highly variable, and especially that our method of measuring results is of necessity unduly subjective. I hope, however, that continuation of these observations over the next few years may allow a more definite conclusion. In the meanwhile we will continue to afford the apparent benefits of steroid therapy to patients with acute disseminated sclerosis excluded from our trial.

In retrobulbar neuritis I am convinced of the value of steroid therapy. The improvement which often seems to follow rapidly on the institution of such treatment in this disease may be due to nothing more than the shrinkage of an optic nerve swollen by inflammatory œdema – a non-specific

symptomatic response quite innocent of any implications as to the allergic pathogenesis of the syndrome. Results are inconstant and some experienced observers remain sceptical. Nearly every case of retrobulbar neuritis recovers spontaneously anyway. Nevertheless many patients recover so rapidly that coincidence seems an unsatisfactory explanation. For example, in one recent case – a girl of 19 almost blind in both eyes for nearly five weeks – vision began to improve within twelve hours of the first injection of ACTH and the patient was able to read large print thirty-six hours later. The treatment of retrobulbar neuritis with steroids would be a perfect subject for a controlled therapeutic experiment, with careful comparative measurements of duration of disablement before and after the institution of treatment and of gradients of visual acuity. It is surprising that no such trial appears to have been carried out in any of the ophthalmic hospitals in this country.

In these acute inflammatory diseases of the nervous system, accurate diagnosis is very difficult. When no therapeutic interference is under consideration a contemplative approach is permissible, but the decision to interfere demands reasonable confidence in diagnosis. To the best of my knowledge I have not made the mistake in this connexion which has always been at the back of my mind – to treat as an acute demyelinating lesion a bacterial meningitis or a cerebral abscess. However, I can recall three serious diagnostic errors in this group of patients. One 35-year-old man with what appeared to be typical bilateral retrobulbar neuritis became stuporous and died under treatment: autopsy revealed an invasive glioma arising in the hypothalamus. One young woman died suddenly from rupture of an intracranial aneurysm a few weeks after partial recovery of an apparently unilateral retrobulbar neuritis. In a third the recognition of an extradural spinal abscess was delayed by the initial attribution of a slowly ascending flaccid paraplegia to a Guillain-Barré lesion.

Polymyositis

Early reports (Shy & McEachern 1951) that 'menopausal dystrophy' was improved by treatment with cortisone were one factor in the emergence of polymyositis (Walton & Adams 1958) as a diagnostic entity – if a somewhat blurred one. This is from every point of view a difficult field. The condition lacks clinical definition and unfortunately the findings on electromyography or muscle biopsy may also be inconclusive. Nevertheless it cannot be gainsaid that there is a considerable group of patients at all ages who manifest non-familial proximal muscular weakness and wasting with or without pain, tenderness, fever or constitutional disturbance, in whom the clinical features of muscular dystrophy may be closely simulated, but whose condition is essentially inflammatory and who show striking and sustained improvement after steroid therapy. Indeed, the genuineness of this therapeutic response is perhaps the main justification for the acknowledgment of this syndrome as a nosological entity. As in the case of other collagen-vascular disorders the best response is usually seen in the more acute cases, but striking improvement is not infrequent even when disability has been severe for several years.

Sarcoidosis

The resolution which may occur in the lesions of sarcoidosis under the influence of steroid treatment sometimes extends to the neurological manifestations of the disorder. Good results are more often seen in the case of cranial and peripheral nerve lesions, but on occasion cerebral and spinal syndromes may improve dramatically. I am indebted to Dr John Simpson of Workington for details of such a case:

Case 1 A 44-year-old woman had been under treatment for atrophic rhinitis for twelve months and during this time slowness of speech, impairment of memory and concentration, and headaches had appeared. In February 1960 she was admitted to hospital with increasing drowsiness and mental confusion. Clinical examination revealed questionable early papillœdema as the only abnormal finding, but the spinal fluid was under increased pressure (250 mm of water) and contained 450 mg of protein, 32 mg of sugar, and 42 lymphocytes per 100 ml. Radiological examination showed some rarefaction of the clinoid processes and some broadening of the mediastinum with enlargement of the root of the left lung. She was transferred to a neurosurgical unit as a case of intracranial tumour, probably metastatic. This suspicion was strengthened by the EEG finding of a consistent focus of delta activity in the right frontal region. Carotid angiograms were negative: ventriculography with air and Myodil showed only obstruction of the foramen of Monro. The patient was considered unfit for a Torkildsen operation and instead a Spitz-Holter valve was inserted, with some apparent improvement in her condition. She was sent home with a hopeless prognosis, slightly better mentally but still complaining of severe headaches.

Re-examined three months later she remained amnesic and inattentive, with persisting dysarthria of cerebellar type. The spinal fluid pressure was lower but its composition remained grossly abnormal. At this stage she developed epistaxis and enlargement of the submandibular glands. The E.S.R. was 40 mm in the hour, Mantoux negative, and biopsy of a gland showed typical sarcoid lesions.

Steroid therapy was begun with prednisolone. Within four days drowsiness had disappeared and by the twelfth day she was mentally clear and cheerful; by the sixteenth she was alert and 'almost back to normal'.

This improvement persists, complicated only by some mooning of the face.

Sometimes the empirical administration of steroids in obscure neurological cases leads to a result equally gratifying but less helpful diagnostically. This was the case in a patient recently seen with Dr T C Studdert at the Cumberland Infirmary:

Case 2 A woman of 26 had a severe subacute meningitic illness with high fever, the spinal fluid being characterized by a lymphocytic pleocytosis (112–300 cells per ml), raised protein content (97 mg/100 ml) and normal sugar and chloride levels. There was right-sided papillœdema without visual defect, the left disc being normal. The Mantoux test gave a 'delayed positive' result. Blood cultures were negative and the patient's condition deteriorated on penicillin and also on isoniazid and streptomycin. During four days' administration of the last two drugs her temperature fell and the spinal fluid showed some improvement, but her clinical condition deteriorated alarmingly: vomiting was intractable and stupor deepened to coma. Comprehensive biochemical studies were normal, and corticotrophin was administered empirically in a dosage of 80 units daily. Improvement began within hours and the next day she sat up in bed and demanded a pork chop. After three weeks' treatment she was well except for persisting unilateral papillœdema. Corticotrophin was gradually reduced and withdrawn. Within twenty-four hours she vomited repeatedly and again lapsed into stupor which remitted dramatically on reintroduction of the drug. During this period extensive virus studies and guinea-pig inoculation had been returned negative. The Kveim test was equivocal. After a further course of treatment with corticotrophin she made a complete recovery and is back at work.

Miscellaneous Uses

Steroids have also been employed in many other nervous diseases. Sometimes, as in the use of local hydrocortisone injection in the carpal tunnel syndrome (Foster 1960), their use has been rational. In this instance the relief almost invariably obtained may be of diagnostic value, but relapse is too frequent to displace operative decompression as the treatment of choice.

Despite the negative observations of Taverner (1954), whose cases were treated within ten days of their onset, the employment of steroids in Bell's palsy appears to be reasonable. It is rare for a neurologist to encounter such cases within twenty-four hours of their onset, but I have treated the few cases I have seen during recent years with prednisolone in full dosage and have been impressed by the rapidity of recovery.

The more empirical employment of these hormones has been without benefit in a considerable group of miscellaneous conditions which includes cerebromacular and hepatolenticular degenerations and other heredofamilial disorders, motor neuron disease, parkinsonism, porphyria, myasthenia gravis, Sydenham's and Huntington's chorea and muscular dystrophy – though some diminution in myotonia has been reported.

The administration of cortisone to patients suffering from virus infections of the nervous system has yielded no benefit and indeed there is experimental evidence that such infections may be facilitated or potentiated by these drugs. Nor have initial claims that they improved the prognosis of cerebral infarction by diminishing post-ictal œdema been substantiated (Dyhen & White 1956).

Neurotoxic Effects of Steroid Therapy

The mineralocorticoid effects of steroid treatment are less conspicious with the newer compounds and from this point of view the treatment of nervous disorders offers no special problems. However, the specifically neuropsychiatric complications of such treatment cause particular difficulty when they occur in patients already suffering from a nervous disease.

In some degree all the steroids seem to facilitate convulsive phenomena and reports that they may actually benefit certain dysrhythmic disorders of childhood (Stamps *et al.* 1959) await confirmation. Caution is indicated where epileptic activity might be anticipated.

Paradoxically, the development of myopathic weakness and degenerative muscle atrophy seems to be an occasional risk of steroid treatment, especially in the case of triamcinolone (Williams 1959). But probably the greatest difficulties arise when psychotic syndromes make their appearance, with or without convulsions. Most of these are affective disturbances, either with depression or excitement, but more complex confusional, hallucinatory or delusional states may be seen and pose the question whether they are due to the disease or the treatment. The frequency with which such symptoms disappear within a few weeks of the withdrawal of treatment suggests that they represent some ill-understood disturbance of cerebral metabolism directly due to the administration of the hormone. The occurrence of a development of this kind raises difficult problems in the matter of withdrawal or intensification of treatment.

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The Use of Steroids in the Treatment of the Guillain-Barré Syndrome

The hypothesis that the Guillain-Barré (G.B.) syndrome is an allergic polyneuritis preceded the use of steroid drugs in its treatment. The idea seems to have been put forward first by Bannwarth (1943) and by Furtado (1950). Furtado called it the 'peripheral form of neuroallergy' and both authors based their belief on the fact that the malady is often a 'second illness' following some apparently trivial infection. They held that the changes in the cerebrospinal fluid (C.S.F.) suggested a transudative process such as is seen in allergic disease, rather than an inflammatory disturbance. The idea is not incompatible with the morbid histological changes. Haymaker & Kernohan (1949) in their very extensive studies showed that the only change during the first few days of the illness is an œdema of the nerve roots. This is later followed by structural changes in nerve fibres and only in the second week does a cellular reaction occur. Scheinker (1949) reported much the same and put forward the suggestion that the œdema caused paralysis by mechanical constriction of the nerve roots where they penetrate the spinal meninges.

The experimental work of Waksman & Adams (1955) finally showed that polyneuritis can be allergic in origin. They produced in animals a polyneuritis comparable to the G.B. syndrome by the injection of sciatic nerve tissue plus an adjuvant. This occurred about two weeks after injection, progressed rapidly for a few days and then, if the animal survived, which was usual, a more or less complete recovery took place. The disease was associated in most cases with a rise of protein in the C.S.F.

This is the background which provided justification for the use of steroids in the treatment of the G.B. syndrome. First reports were unfavourable (Shy & McEachern 1951, Merritt 1952). but since 1952, many cases have been recorded in which their use has seemed to cure the condition, often quite dramatically. In this country the first treated cases were those of Clarke *et al.* (1954) and Hay (1955), both of whom seemed to benefit. In 1957 Jackson, Miller & Schapira reported 5 cases and I reported 7 cases (Graveson 1957). Of Dr Miller's cases, 4 improved immediately, 1 dramatically, and in the 5th pain ceased within twenty-four hours and improvement began after one week. Of my 7 patients, 1 of whom had two attacks, improvement began either within one or two days or in the second week of treatment in seven attacks; in the 8th the response was poor and the patient deteriorated when the dose of cortisone was reduced, which in any case I thought in retrospect had been inadequate. Dr Miller and I came to the conclusion that steroids might only be effective in reducing the initial œdema of nerve roots and that once degeneration of nerve fibres had occurred, recovery could only be by regeneration, which could hardly be expected to be hastened by these hormones. I was able to show that mild cases improved quickly and in severe cases, where some groups of muscles were completely paralysed recovery in muscle groups not so severely affected occurred in the same time as in the mild cases.

The assessment of therapeutic success as opposed to spontaneous recovery is difficult, and indeed it has been suggested that in individual cases it is impossible. I do not think so. Too many cases have been reported in which improvement has begun within a day of the onset of treatment to make it probable that this is mere coincidence. Others show no improvement for several days and then a rapid recovery occurs. This usually happens in the second week of treatment and these I regard as showing a good response. But more important, perhaps, in evaluating the efficacy of treatment is the relapse which happens when drug dosage is reduced too soon. Previously recovered muscles may weaken within twenty-four hours and recover equally quickly when the dose is increased again. It is therefore most important that patients be examined daily at this stage. These drug withdrawal recurrences are to my mind the most conclusive evidence we have that steroids are effective in modifying or curing this disease.

The difficulty of assessment arises because of the relative rarity of the disease, its variable severity and duration and the impossibility of organizing a controlled trial of treatment. In this context the unique case described by Austin (1958) is of considerable importance. His patient was a man of 40 who, over a period of five years, had no fewer than 20 bouts of polyneuritis. Consistently, throughout this period, he relapsed when steroid therapy was reduced or withdrawn, and equally consistently improved when treatment was given in adequate dosage within periods of five to eleven days. When placebos were substituted, relapse occurred quickly. It was found that ACTH, cortisone and prednisone all had the same

predictable effect. Here the patient acted as his own control and he clearly had a steroid-sensitive polyneuropathy. Austin makes the further point that the difference between acute and chronic relapse in this patient appeared to be related to the dose of steroid withdrawn and he suggested that the difference between acute and chronic polyneuropathy may lie in a difference in host resistance, due perhaps to the amount of steroids biologically present and active. If this is so, then we might expect that the most acute and widespread cases of the G.B. syndrome would show a poorer response to steroids than the less severe ones using a standard dose schedule. My experiences since 1957 tend to support this idea. I have seen a further 14 cases, making a total of 21 cases, or 22 attacks in all, for one patient had two attacks. In 1958, a change in oral therapy was made from cortisone to prednisone and the routine has been to give 60 mg daily for two days, then 40 mg daily for two days, then 20 mg daily for as long as necessary. In severe cases with bulbar and respiratory involvement initial treatment has been by intravenous hydrocortisone hemisuccinate 100 mg twice daily for two or three days, followed by oral prednisone.

The results are quite simply expressed—in 14 attacks steroids were helpful and in 8 they were not. Of the 14 attacks which responded, 12 improved considerably in two weeks, the improvement starting either at once or being delayed for not more than a week. In the other 2 attacks, no definite improvement occurred in this period, but there was a drug-withdrawal relapse which improved on increasing the dose of prednisone, and they are therefore included in this group.

Of the 8 patients who did not improve, 2 died. One was a man of 69, who died suddenly and unexpectedly on the eleventh day of treatment, when there had already been some muscular improvement, of a presumed cardiac arrest or arrhythmia from myocarditis. The second patient was a woman of 69, who died on the fourth day of her illness. She had a very rapidly extending paralysis, necessitating admission to a respiratory unit on the third day for tracheostomy and intermittent positive pressure respiration. Intravenous hydrocortisone was given for the last twenty-four hours, without effect.

Of the other 6 patients in this group, 5 were severe cases on admission, and of these 2 did not improve within two weeks, but the disease did not progress once prednisone had been started; 3 deteriorated after treatment was begun and 2 of these required tracheostomy and assisted respiration. The 6th patient was the failure in the 1957 group.

These 8 failures contained the 7 worst-affected patients and included all the 5 patients who had respiratory involvement. There seems to be no correlation between the response to treatment and the time-interval between the onset of symptoms and the onset of treatment. What does seem of importance is the extent of the paralysis and its severity at the time therapy is begun. Thus only 2 patients mildly affected at the onset deteriorated, and I apply 'mild' to any case not showing complete paralysis or flicker movements in any one muscle group. This is what one might expect if the condition is allergic and if steroids will reverse the condition at the stage of root œdema.

The problem still remains whether the G.B. syndrome is a single disease-entity or whether it comprises diseases of varied ætiology. It hinges on why a third of the cases are refractory to steroids. Is this because they are not allergic in origin, or is it because too small a dose has been given, or because structural changes have occurred? For the moment the matter rests on a belief rather than a proof, and I believe that most cases are allergic in origin. This hypothesis, however, has tradition to contend with in the form of the equally hypothetical infective theory. Guillain has always believed that this is the cause of his syndrome. As for the allergy idea, 'I cannot consider this very vague pathogenesis', he wrote (1953), and 'I do not agree with it from any point of view'. Of steroids, 'It seems to me', he said, 'that the habitually favourable prognosis of the G.B. syndrome does not justify these injurious medications'. The past few years have shown, however, that they are the only effective means of treating the condition.

I am grateful to colleagues in the Wessex Region who have referred patients to me.

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Dr Gerald Parsons-Smith (*London*) stressed the value of steroid therapy in cranial arteritis. As the first sign of this disorder may be the painless occlusion of a cerebral or a retinal artery, he recommended that all patients over the age of 55 who sustained such a vascular insult should be given, immediately, a trial course of prednisolone extending over a week.

Section of the History of Medicine

President K D Keele MD

Meeting April 5 1961

President's Address

Three Early Masters of Experimental Medicine – Erasistratus, Galen and Leonardo da Vinci

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It commonly happens that realities exist in the history of human affairs long before they acquire the dignity of a name. This is true of experimental medicine. Since the concept of experiment came into general acceptance only after the sixteenth century the word did not appear in our vocabulary until that time, and it has become customary to refer the origins of experimental medicine to that era. It has, indeed become so much an accepted practice to deny the ancient Greeks and men of the Renaissance the experimental approach that I feel it is time that this attitude should be reviewed and readjusted.

How do we define the term 'experimental medicine'? I know of no better definition than that of Claude Bernard (1957), who called it 'induced observation'. Comparing the methods of observation and experiment Bernard said: 'With observation and experiment a fact is simply noted; the only difference is this – as the fact which an experimenter must verify does not present itself to him naturally he must make it appear, i.e. induce it for a special reason and for a special object.' Thus an experiment always involves a preconceived idea, a technique of planned procedure, and a comparison, which we nowadays call a control. If the preconceived idea is vague the experiment consists in essence of merely looking to see. As Bernard says: 'Groping experiments which are very common in physiology and therapeutics . . . may be called *experiments to see*.' Lest we should underrate this kind of approach it is to be noted that it was from just such an 'experiment to see' that Bernard himself made the discovery of the mode of action of curare. But, as Bernard stresses, this kind of experiment should be done only as a means of acquiring more precise preconceived ideas upon which to base more intelligent experiments.

It is most often in the skilful design and technical performance of the induced observation or experiment that the mastery of the experimenter is revealed. This is the part of the process which is most personal though its results, with their interpretation, must be most impersonal. And here lies the gap between the tidy-minded theorists of Baconian inductive logic and the often untidy artists of creative science, whose unique work is to provide those firm observations upon which inductive thought can be based. Men with the power of such achievement I call masters of experimental medicine; and it is for this capacity I propose briefly to review the work of Erasistratus, Galen, and Leonardo da Vinci.

The commonest and the most fruitful of the preconceived ideas applied to experiment in medicine are those derived from the basic sciences of the day. Of chemistry there existed none in the days of the three men we are considering. But an elementary form of physics founded on the principle of the *horror vacui* extended far back even into pre-Hippocratic times. Indeed this principle was used by the Hippocratic writer of the work, Ancient Medicine, when he asks: 'Which structure is best adapted to draw and attract to itself fluid from another body, the hollow with the wide opening, the solid and round, or the hollow and tapering?' (Adams 1849) and he answers the question through the analogy of cupping, concluding that it is the bladder, the head, and the womb, which are hollow organs with a long narrow entrance.

Strato

Intensive experimental analysis of the phenomena of the *horror vacui* was carried out by the man who was Head of the Lyceum at Athens, after Aristotle and Theophrastus about 300 B.C. This man, Strato of Lampsacus, has suffered eclipse

through the complete loss of his works. It was only in 1893 that Hermann Diels unearthed a fragment of his work from which we can gain some idea of Strato's experiments on hollow vessels; from this I shall quote. First demonstrating that empty vessels containing air cannot be filled with water, Strato went on to show that the particles of air in a vessel can be compressed by positive pressure and thinned by negative pressure. Strato stated it thus: 'Vessels which are generally believed to be empty are not really empty but are full of air. Now air consists of minute particles of matter for the most part invisible to us. Accordingly if one pours water into an apparently empty vessel a volume of air comes out equal to the volume of water poured in. To prove this make the following experiment. Take a seemingly empty vessel. Turn it upside down, and plunge it into a dish of water. Even if you depress it until it is completely covered no water will enter. This proves that air is a material thing . . . now bore a hole in the bottom of the vessel. The water will then enter at the mouth while the air escapes by the hole' (Farrington 1953). So far the experiment is almost a repetition of one described by Empedocles in 450 B.C., but Strato further develops his experiments. 'If', he says, 'the particles of air are separated from one another, with the creation of larger empty spaces between them than is natural, then their tendency is to draw together. Take a light vessel with a narrow mouth, suck out the air, and take your hands away. The vessel will remain suspended from your lips because the void will tend to pull the flesh in . . .' Strato then goes on to show that vacua exist in nature in very small scattered form, by taking a large metal sphere into which a narrow copper pipe was inserted. 'One who puts his lips to the pipe can blow a great quantity of air into the sphere without any of the contained air escaping. This constitutes clear proof that the particles of air in the sphere are compressed into the vacua between the particles.' 'If the reverse experiment be tried, a great quantity of air in the sphere can be sucked out without any other air getting in. This experiment conclusively demonstrates that the formation of a continuous vacuum takes place in the sphere. Summing up we may say that all bodies consist of tiny particles of material between which are interspersed vacuums smaller than its parts . . . it is only in so far as one of these substances departs that another can enter to occupy the empty space.'

The childish simplicity of these experiments may make us smile, but this must not be allowed to obscure for us their importance. The 'tiny particles' and the vacuums were for the advanced thinkers of 300 B.C. what the muons and pions are for our own time.

Erasistratus

I have cited these experiments of Strato since he was living in Alexandria at the same time as his younger contemporary Erasistratus upon whom he exerted a great influence both with regard to the results of his experiments on air and the nature of his experimental method. Erasistratus was first an anatomist whose descriptions of the heart and brain evince a knowledge of detail that was not reached again until the days of Vesalius. But his greater contribution was towards experimental physiology and pathology. Unfortunately, as with Strato, all his works have been lost; they were probably destroyed when the great library of Alexandria was burnt down. We have our accounts of his work therefore only through the scrappy references to him in the works of his successors, chiefly Galen, and Galen was stimulated to bitter criticism of Erasistratus for the purely mechanical nature of his predecessors' physiological theories. But Galen tells us enough to make it evident that Erasistratus performed innumerable experiments on animals which were designed to apply Strato's science of pneumatics to human physiology and pathology. It was for example, on this pneumatic basis that Erasistratus conceived of air being drawn into the lungs by the negative pressure within the thorax on inspiration. This sound explanation he unfortunately pushed too far. He thought that similar negative pressure extended into the heart in diastole, air thus being drawn through the pulmonary veins into the left ventricle. Moreover, assuming that arterial diastole was an active movement, he found the arteries to be full of air so attracted from the left ventricle into their lumens. Thus he reached the conclusion that in health the arteries contain air, not blood. Flesh Erasistratus considered to be composed of the terminal interwoven network of arteries, veins and nerves, and thus he came to interpret muscle tone and action as derived from the tension of air within the small arterioles. Blood he considered to be conveyed in the veins and right ventricle alone; only in disease did it leak over through peripheral anastomoses into the arteries, where it gave rise to the heat, swelling and pain of inflammation. The movements of all the body fluids Erasistratus found by his experiments to be due to pressure differences. In the stomach digestion was achieved by heat and mechanical pressure; nourishment reached the liver by being squeezed along the portal vessels; bile was formed in the liver by filtration from the blood; urine was formed by filtration through the kidneys. In all his physiological theories Erasistratus persistently ignores the humours, apparently never even discussing them. Herein lies the cause of Galen's frequent and bitter references to his work.

Few indeed are the instances where we have the opportunity of hearing Erasistratus speak for himself, but we do have a brief comment he made on the subject of research. 'Those', he says, 'who are altogether unaccustomed to research are, at the first exercise of their intelligence befogged and blinded, and quickly desist owing to fatigue and failure of intellectual power, like those without training who attempt a race. But one who is accustomed to investigation, worming his way through, and turning in all directions, does not give up the search his whole life long. He will not rest but will turn his attention to one thing after another which he considers relevant to the subject under investigation, until he reaches the solution to his problem' (Farrington 1953).

Two examples must suffice to illustrate the experimental genius of Erasistratus; one shows his enthusiasm, and one his skill. Celsus tells how Erasistratus, with his colleague Herophilus, opened men whilst these were still breathing, and 'observed parts which beforehand Nature had concealed, their position, colour, shape . . . For when pain occurs internally, neither is it possible for one to learn what hurts the patient unless he has acquainted himself with the position of each organ or intestine; nor can a diseased portion of the body be treated by one who does not know what that portion is like'. Here Erasistratus' experimental zeal has brought him condemnation on ethical grounds throughout the ages. Even that enthusiastic advocate of vivisection, Claude Bernard, condemns him. But it does clearly reveal to us the experimental nature of Erasistratus' attack on problems of physiology and pathology.

His skill is better illustrated by his attempt to show that evaporation of invisible particles from the body continuously takes place. It is described by the writer of the manuscript called Anonymus Londinensis, thus: 'If one were to take a creature, such as a bird . . . and were to place it in a pot for some time without giving it any food, and then weigh it with the excrement that visibly has been passed, he will find that there has been a great loss of weight, plainly because, perceptible only to the reason, a copious emanation has taken place' (Jones 1947). This loss of weight Erasistratus claimed was replaced by nutriment and breath. Thus he anticipated the quantitative weighing experiments of Sanctorius in the seventeenth century, nearly 2,000 years later.

Galen

One measure of the greatness of Erasistratus as an experimenter consists of the innumerable experiments undertaken 400 years later by Galen to refute his results. Indeed it is in this mission that Galen often reveals his own experimental genius, an aspect of his work which has for too long been swallowed up by the dark complexities of Galen the dogmatist, the view of him which has become traditional.

Galen in fact gave a great deal of attention to methods of acquiring medical knowledge. His first work, written when he was 20 years old was entitled 'Medical Experience'. It was devoted to a study of the methods of the dogmatists and empiricists, and sanely concludes that the best method in medicine combines something of both. Experiment Galen specifically includes as a mode of medical experience and he is under no illusion regarding the origins of some of the preconceived ideas of the experimenter. In his work 'On the Medical Sects' he writes: 'What is called improvised experience is when one deliberately tests something that has been suggested by dreams or the like. Further there is another kind of experience, the imitative; in this something which, occurring either by nature, chance, or improvisation, has proved helpful or the reverse, is tested anew in the same diseases by Experiment. . . . Having imitated, not once, nor twice, but repeatedly, the treatment which proved salutary on a former occasion, and having found it has the same action . . . they give a fact like this the name theorem, deeming it now worthy to form an integral part of the medical art.' Such a collection of theorems Galen states is known as Medicine. These theories are built up, he affirms, largely by analogies. Every transition of this kind, i.e. by analogy, he describes 'as a road to discovery, but', he adds, 'Experiment is needed before it actually becomes a discovery'.

It will be seen that Galen approaches Francis Bacon in his comprehension of the gradual inductive method. Unlike Bacon, however, Galen *could* perform experiments as well as think about them. His knowledge of anatomy from personal dissection of animals was vast; man was the animal of which he had least direct knowledge. He reports dissection, or vivisection, of pigs, goats, sheep, apes, horses, asses, mules, cows, lynxes, stags, bears, weasels, mice, serpents, fish, birds, and at least one elephant; modestly confessing that he had not dissected ants, gnats or fleas. It is a range which vies with that of Harvey.

As an anatomist Galen revealed structures whose function he wished to test. To this he was particularly stimulated by the work of his predecessor Erasistratus. His method was for the most part simple. Almost all his experiments in physiology were based on the principle of ablation; he cut nerves and muscles; he tied tubes; and observed the results.

Experimental brilliance does not necessarily coincide with important results. It is indeed in

one of his least momentous experiments that he best displays his experimental mastery. Asclepiades, his predecessor as a famous physician in Rome, had asserted that the excretion of urine was directly into the bladder from the blood. Galen set out to demonstrate that this was the function of the kidneys. He describes his procedure thus in his work 'On the Natural Faculties':

'Now the method of demonstration is as follows. One must divide the peritoneum in front of the ureters; then secure these with ligatures; and next, having bandaged up the animal, let him go (for he will not continue to urinate). After this one loosens the external bandages and shows the bladder empty, and the ureters quite full and distended – in fact almost to the point of rupturing. On removing the ligatures from them one plainly sees the bladder becoming filled with urine. Then, before the animal urinates one has to tie a ligature around its penis, and then squeeze the bladder. Nothing goes back through the ureters to the kidney . . . One now loosens the ligature from the animal's penis and allows him to urinate. Then one ligates one of the ureters and leaves the other to discharge into the bladder. Allowing some time to elapse one now demonstrates that the ureter which was ligated is obviously full and distended, whilst the other, that from which the ligature has been taken, is itself flaccid, but has filled the bladder with urine. Then again one must divide the full ureter, and demonstrate how the urine spurts out of it, like blood in the operation of venesection; after this one cuts through the other ureter also, and both being thus divided one bandages up the animal externally. Then, when enough time seems to have elapsed, one takes off the bandages; the bladder will now be found to be empty, and the whole region between the intestines and the peritoneum full of urine, as if the animal were suffering from dropsy. If anyone will test this for himself on an animal I think he will strongly condemn the rashness of Asclepiades.'

The more closely one examines this series of experiments the more one must admire their beautiful design, and the careful use of control observations at each stage, let alone their superb technical skill in animal experiment. It is still being written by modern historians that the ancients never understood the principle of control experiments; surely it is quite clear from this example, Galen did.

The exhibition of such experimental skill on a problem involving the flow of fluid between viscera leads one to enquire how Galen fared when he directed his attention to the flow of blood into and out of the heart, for he worked hard on this problem experimentally. The exposure of the beating heart and lungs in living sheep and pigs he found to be of great technical difficulty, death of the animal from pneumothorax being only too common. He did however eventually achieve this, and after describing his methods in meticulous detail, and with evident pride, Galen says in 'On Anatomical Procedures': 'When the heart is exposed, your task is to preserve all its functions unimpaired, as in fact they are, so that you can see the animal breathing and uttering cries and, if loosed from its bonds, running as before . . . And what is strange in that? The slave of Maryllus, the mime-writer, whose heart was once exposed, was cured and still lives . . .' and Galen goes on to describe the case of this slave who had a chronic osteomyelitis of the sternum, in whom he successfully removed the affected bone, so exposing the heart, without producing a pneumothorax.

With the heart of the animal exposed by removing the sternum, Galen examined it for the relation of its systole and diastole with the movements of the main blood vessels. But he could no more analyse this in the quick-moving heart of the pig than Harvey could 1,500 years later. Galen tries to elucidate the problem by tying the pulmonary vein, but at each attempt he produces a pneumothorax. 'It is not possible to ligature the course of the vessel [pulmonary vein]' he laments. 'It can be done round the base of the heart, but the animal dies at once.' He is baulked; he has reached the limit of his technical skill and so he failed to break Erasistratus's idea of active cardiac diastole. How could he have overcome this obstacle? We know from his experience of comparative anatomy that he had dissected serpents. Here was the way, but he did not think of it. It was not until Harvey selected snakes for vivisection because of the slow action of their hearts that systole and diastole of the heart and main vessels were successfully analysed. This is a momentous example of the importance in experimental medicine of choosing the right animal.

But Galen did establish, by an experiment which Harvey repeated, that, contrary to Erasistratus, the arteries contained blood in life. This meant communication between veins and arteries. Ignoring the peripheral anastomoses between veins and arteries which Erasistratus had postulated he sought for some other communication between them, and found it in the 'invisible pores' which he suggested communicated between the right and left ventricles through the septum of the heart, whereby in diastole blood was sucked from the venous into the arterial tree. It was a logical but unhappy hypothesis the consequences of which need no elaboration.

The most momentous of Galen's experiments were those he performed on the spinal cord and nerves. Many of these were prompted by a desire to analyse the movement of respiration and phonation. These experiments on pigs he summarizes as

Fig 1 *Galen's public demonstration of division of the recurrent laryngeal nerve in the pig. From the Froben Edition of Galen's Works, 1586*

follows: 'If you sever [the spinal cord] completely between the 3rd and 4th cervical vertebræ, the animal at once ceases to breathe. Not only does the thorax become motionless, but also the whole body below the section. If [section is made below] the 6th cervical vertebra, all the muscles of the thorax become motionless immediately and the animal breathes in only by the diaphragm. Transverse sections below this vertebra permit other parts of the thorax to move . . . The further you advance towards the lower vertebræ the more muscles of the thorax will you leave active. However this does not happen to the pair of nerves entering the phrenes [diaphragm]; when all the other nerves are destroyed the animal breathes with diaphragm alone. When the spinal marrow is cut in the middle, straight downward, it does not paralyse either [set] of the intercostal muscles, or those in the loins or legs. When cut transversely, if only the half is severed, all the nerves on that side are paralysed in series.' Not until Brown-Séquard and others repeated these experiments in the middle of the nineteenth century, were Galen's brilliant observations repeated and appreciated.

In the course of his neurological experiments Galen had the good fortune to cut the recurrent laryngeal nerve of a squealing pig; the sudden silence of the consequent aphonia was too dramatic to be missed. This discovery of the innervation of the vocal cords gave him one of his proudest moments. His friends hired a special hall for him to demonstrate the experiment before the foremost philosophers of Rome. One can almost hear Galen saying to them; 'I want you to realize that what I am describing was discovered by me, that no anatomist knew a single one of these particulars and hence made many errors in connexion with the larynx' (Walsh 1926). This moment, illustrated in the Frohen Edition of Galen's works in 1586, shows convincingly how fashionable physiological experiment had become in the Rome of Galen's day (Fig 1).

Dissatisfied with the purely physical explanations of physiology advanced by Erasistratus, Galen developed the theory of the humours to be found in some of the Hippocratic works. In these humours, and in his postulates of what he called 'natural faculties' such as attraction, adhesion, alteration and assimilation, it is possible to see him reaching out to a kind of hypothetical chemistry. Many of his experiments, undertaken to demonstrate these forces were ingenious, but necessarily erroneous. To take one example, from his investigations of the act of swallowing: ingeniously he demonstrates that after either transverse or vertical incisions through the coats of the œsophagus swallowing can still take place. From this in 'On the Natural Faculties' he deduces that, 'the stomach draws food to itself by means of the gullet as though by a hand. Just as we ourselves in our eagerness to grasp something stretch out our whole bodies along with our hands, so also the stomach stretches itself forward along the gullet, which is, as it were, a hand'. In such experiments, to demonstrate the faculty of 'attraction', Galen only too clearly illustrates the dangers of the experimental method in the service of a premature general theory. Such a use of experiment helped to consolidate that massive body of Galenic dogma which was found so impregnable by his successors through the centuries.

Leonardo da Vinci

For some mysterious reason the fashion for experiment amongst the intelligentsia of Rome died with Galen. And until the Renaissance the quest for experimental knowledge, apart from isolated examples from men like Roger Bacon, seems to have been quenched by the Christian and Moslem faiths. One of the first to break through this barrier into experiment was Leonardo da Vinci, whose methods, like so many of his other activities, were unique. There are three main

reasons for this; first, his approach to experiment on animals was primarily that of the artist; secondly, Leonardo was an anti-vivisectionist; and thirdly his language of record was dominantly visual.

Of the artistic approach to anatomy and physiology at this time one need say no more than that it supplied the impulse to fresh observation which was not forthcoming from the medical profession. This Leonardo shared with his contemporary artistic colleagues. His anti-vivisectionist views are however less well recognized. His deep repugnance to killing animals is expressed in the words: 'Our life is made by the death of others. Man and animals are sepulchres . . . making life out of the death of the other; taking pleasure in the misery of others, and making themselves the covering of corruption' (Richter 1955). These sentiments led him to be a vegetarian in his diet, and to abjure vivisection in his experiments. Apart from the pithing of a frog, not one of his experiments in physiology was performed on living animals. An apparent exception, the well-known observations of the movements of the knife or 'spillo' in the hearts of dying pigs, were made by him as he watched the routine slaughtering of these animals in the abattoir. Vivisection is considered by most physiologists as the *sine qua non* of experiment. How then did Leonardo approach his biological experiments?

Leonardo nowhere discusses his methods as such, and one has to construct his approach to experiment from the disorder of his notes. Here he repeatedly insists on the necessity of personal observation, on the necessity of mathematics, by which he means geometry, and on the application of the laws of physics, particularly mechanics. 'Mechanics', he writes, 'is the paradise of the mathematical sciences because by means of it one comes to the fruits of mathematics' (Keele 1952). It was through his deep comprehension of the geometry of forces that he was able to make those conversions and transmissions of power which crystallized out in his many inventions of machines, such as water-mills, printing presses and lathes. It was through his understanding of the geometry of forces that he anticipated the principle of inertia, so that it was commonly named after him until Galileo and Newton stated it in clearer mathematical form. The same holds for his conception of the force of gravity and the parallelogram of forces. It was through his geometrical vision that he could see that: 'Just as a stone thrown into the water becomes the centre and cause of various circles, and the sound made in the air spreads in circles, so any body placed within the luminous air spreads itself out in circles and fills the surrounding parts with an infinite number of images' (Richter 1955). Each of these statements is verified by many painstaking experiments. Thus it was he reached a conception of the wave-motion of light and sound.

But of all media water was his favourite, for this gave him the clearest visual evidence of the dynamic geometry of active forces; and water was his main professional pre-occupation as an engineer in charge of the maintenance of the waterways of Lombardy. In the Martesana and Ticinello canals he could see the formation of vortices, draw their shapes, and construct models for experiment on their variations.

When he came to the study of the human body he brought with him this mass of experimentally acquired knowledge shaped into mechanical principles. For Leonardo the movements of the muscles and bones were opportunities for application of the laws of the lever, and the movement of the blood was an exercise in hydrodynamics. Discussing how to present his anatomical studies he writes: 'Arrange it so that the book of the elements of mechanics, with examples, shall precede the demonstration of the movement and force of man. . . . By means of these you will be able to prove all your propositions' (Keele 1952). His approach was thus much more akin to that of Erasistratus than Galen. Indeed chemistry existed for Leonardo no more than it did for Erasistratus or Galen; the alchemy of his day Leonardo despised and abjured.

Thus one may look upon Leonardo's anatomical studies as the preliminary investigation of an apparatus capable of exerting forces as a machine. Throughout them all one can see his pre-occupation with the mechanical significance of what he dissects. Having obtained the essential knowledge of the mechanical principles of the dissected part, he takes it outside the body by creating his imitation of it in the form of a model. Here he finds freedom in studying and controlling variables necessary to reach their underlying principles of action. He applied this method, for example, to the study of the eye in relation to light (Fig 2), making models of the cornea and lens, and placing his own eye in the position of the optic nerve, where he considered the sensitive part of the retina should lie. It was during these experiments that he discovered the camera obscura, which was constructed merely incidentally as part of his model of the human eye.

Thus Leonardo's technical experimental skill was *not* that of the vivisectionist; it was that of the sculptor and engineer. His experiments represented for him reproductions of the powers of Nature in the same way as his finest paintings were created as symbols of Nature and her Laws.

Leonardo's methods of recording his experiments were more unusual even than his methods of making them. He was very much aware of the

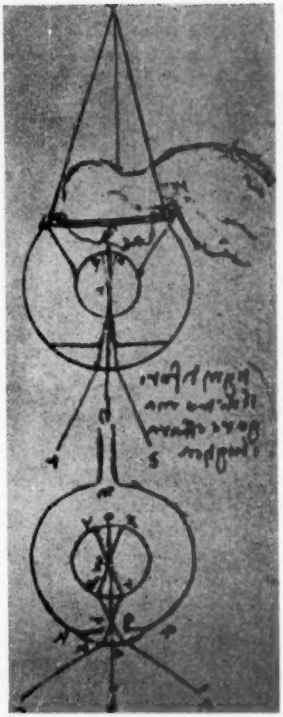

Fig 2 *Leonardo's construction of a model eye. His own eye is placed at the position of the optic nerve, as depicted in the figure alongside. The large glass globe, filled with water, has the solid glass lens suspended within it. The whole is made to be suspended so that the head of the observer can be fitted into it. (MS D 3v, Institut de France, Paris)*

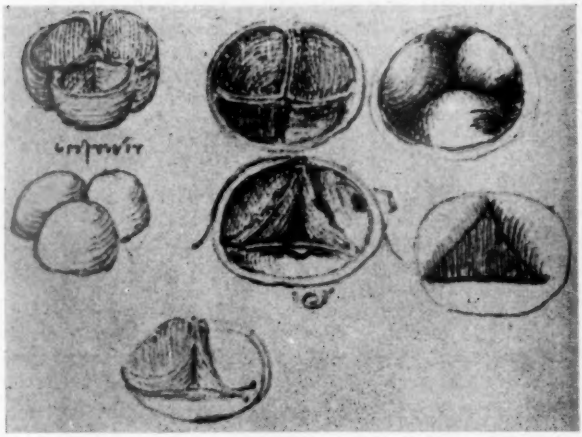

Fig 3 *Aortic valves, removed, and studied from above and below, open and shut. The orifices of the coronary arteries are clearly shown, and the triangular aperture of the opened valve cusps emphasized. (QA II 9v)*[1]

insufficiencies of word-language. Languages, he asserts, have many words for the same thing; they vary from century to century, from one country to another; languages are liable to pass into oblivion, and they are mortal like all created things. In contrast he repeatedly affirms the advantages of visual images for conveying scientific information. Only in this way, he asserts, can one speak a direct, universal and permanent language which circumvents errors of translation and verbal misunderstanding. It is for this reason that whole pages of his manuscripts are often found full of drawings only, with no explanatory words. Often his thought is to be found in isolated diagrammatic sequences. When he does use words he is often repetitious, striving to reach his meaning by writing passages not once but two or three times. This he does more often towards the end of his life, particularly in his work on the heart. This choice of visual images as language serves to make Leonardo comprehensible to-day in unique fashion; but it also limited his formulation of abstract laws, reducing him to the description of details and particulars. As a result his scientific achievement has been severely criticized on the grounds of his lack of great generalizations.

All these aspects of Leonardo's approach to experimental physiology are evident in his work on the heart. Of all organs of the body this fascinated him most, for its hæmodynamic problems offered a direct challenge to his experience gained from his work on the movement of water. For these reasons, and because a series of experiments which he made on the heart and aorta have some contemporary interest, I shall confine illustration of his methods to this work.

Early in his anatomical studies he satisfied himself that, contrary to Galen's opinion, the heart is a muscle pump, and that its movements of systole and diastole are governed by the same mechanical principles as other muscles. This led him to make intensive study of the heart valves, all of which received individual attention. The three leaves of the tricuspid valve, for example are drawn unrolled, as it were, in order to examine the part played by the cordæ tendinæ and papillary muscles in opening and closing the orifice. But the aortic valve received more intensive study than any. Its cusps were drawn *in situ*, open and closed, and removed from the body (Fig 3). The triangular shape of the open aortic orifice was repeatedly noted, and the dilatation at the root of the aorta, named after Valsalva, was carefully drawn.

[1] QA = Quaderni d' Anatomia (Vangensten *et al.* 1911-16)

Fig 4 *The page of manuscript on which Leonardo gives constructional diagrams of an artificial aorta and valves. The scheme for making a cast of the aorta and valves is enclosed in the sketch (top right). The constructional diagrams extend to the left, and upwards on the left margin of the page. The written words make no comment on the diagrams. The remaining figures show the return stream of blood by which the aortic valves are closed. At the top of the page is drawn the buckling of the valve cusp which would occur if the blood pressed straight down on the cusp. (QA II 12 r)*

Having satisfied himself of the shapes and relations of this region of anatomy, Leonardo proceeded to his next stage of experimental investigation, that of creating a working model of the parts, in imitation of Nature. Now this is the very problem upon which so much work is being done to-day, when it has become possible to approach the aortic valves surgically. Leonardo's attempt to make an aortic prosthesis may thus be looked upon as an anticipation of what is being attempted to-day. It may be that present day workers could gain some useful information from his efforts.

First Leonardo made a cast of the base of the aorta, a task of great difficulty even for a man of his manual dexterity. He began by making a wax cast of the aorta; over this he made a hollow cast of gypsum. This he lined by a sheet of blown glass. He makes a special note that the wax must be poured right into the heart through the valve orifice, or 'gateway of the heart', as he calls it, 'to see its true form'. On this particular page of manuscript (QA II 12r) (Vangensten *et al.* 1911-16) there are several drawings of the stages of this construction of the aortic valves, of which he gives no verbal description at all (Fig 4). Because of this they have received no notice from commentators. But his procedure becomes clear if the drawings are read from right to left, which is Leonardo's usual sequence of diagrammatic thought, since he was left handed, and always wrote his words in this direction. Here can be seen his construction of a tripartite flange on a circular base which is then inserted into a tube. The vertical flanges are then cut off and pared down to the hollowed shape corresponding to three aortic cusps . . . but the clumsiness of word description compares badly with the clarity of Leonardo's drawings. This model of the valves was then incorporated in the glass mould of the root of the aorta, 'To see in the glass what the blood does in the heart when it shuts the opening of the valves' (Keele 1952).

On another page (QA IV 11v) (Fig 5) he illustrates his tripartite model divided longitudinally into its three separated parts. In this model he has exaggerated the sinuses of Valsalva, and widened the base into a shape which is shown fitted to the left ventricle of a bull's heart. He also shows by a series of constructional diagrams how the model is designed. His only verbal comment on them is the few words placed between the figures; 'Fa questa prova di vetro a movici dentro a cise panicholo' 'Make this glass trial (experiment) and move in it the pannicles (valves)' (Keele 1952, p 81).

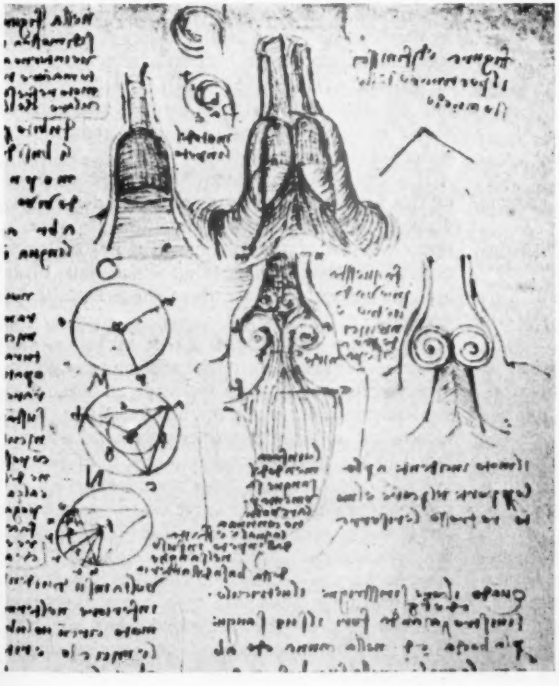

Fig 5 *Leonardo's model of the aorta and its valves, divided into three parts to show its mode of construction; the design is represented diagrammatically below in three circular figures. The closure of the aortic valve cusps by the return eddies of blood is shown in the central figure. Beside this are the words 'fa questa prova di vetro e movici dentro a cise panicholo'. (Make this glass-trial and move in it the pannicles). (QA IV 11v)*

Fig 6 *Studies of the movement of fluid through pipes of different shapes. At the top, fluid emerging from round-ended pipes is drawn. Below, diagrams of the triangular aortic orifice are accompanied by sketches of the fluid trajectories passing through such an orifice.* (*QA IV* 11*r*)

So much for his construction of the model of the aorta. How did he propose to 'make his trial' with it? He uses the same methods that he has practised for so many years in his studies on the movements of water in rivers and streams. Amongst these are to be found several in which he makes model channels of glass, in which, in order to follow the fluid veins he notes: 'Let the water that strikes there have millet or fragments of papyrus mixed with it, so that one can see the course of the water better from their movements.' Elsewhere he suggests dropping in a few grains of panic grass, 'because by the movement of these grains you can quickly know the movement of the water that carries them with it' (Keele 1952, p. 80). Such were the methods he used to observe the movement of fluid through his model aortic valves.

He begins the observation of such movements with the simplest case, that of water emerging from a round-ended pipe (Fig 6). He then modifies this by making the pipe of triangular section with dilatations corresponding to the sinuses of Valsalva; and he finds that the fluid forms three vortices. This circular motion of the blood he considers responsible for the dilatations at the base of the aorta which Leonardo calls the 'hemicycles', and we the sinuses of Valsalva. Repeatedly Leonardo demonstrates that this returning circular motion of the blood closes the aortic valve cusps by a lateral not a vertical force, pushing them against one another like three bellying sails. This returning stream of blood, 'beats the valves with composite motion', he writes, 'raising and stretching them; and shuts them against the opposite valve cusps'. The valve cusps cannot be closed from above, he asserts, since this would buckle the cusp upon itself. He makes many drawings of this mode of closure of the aortic valve. He even goes so far as to consider the velocity of the blood in the various stages of its movement through the aortic valve. From his experiments on water he had discovered that the velocity of flow varies inversely with the diameter of the channel: 'the greater the velocity the smaller the dimension of the passage', he writes, 'as demonstrated in the 3rd part of my "Discourse on Waters" ' (Keele 1952, p 84). Thus he deduces that the rate of blood-flow through the narrow aortic valve must be greater than that in the wider hemicycles.

It is almost incredible that Leonardo should see all this from the movements of the seeds of panic grass in his glass models of the aorta. But if he is right, closure of the aortic valves has rather a different mechanism from that which most of us imagine. How far can these observations be verified?

Some years ago with Mr I K R McMillan and his remarkable apparatus for studying the movements of the aortic valves we made an attempt to see such currents as Leonardo drew. But, technically the apparatus was not suitable and we failed to see the movements of the fluid clearly. We did however note how accurate were Leonardo's drawings of the valve cusps in the open and closed positions. A comparison of the drawings and photographs from Mr McMillan's (1955) cinephotographic series (Fig 7) makes it clear that Leonardo must have seen these cusps in motion in order to draw their wrinkled edges so accurately; it is an appearance which is not present in the closed valve after death.

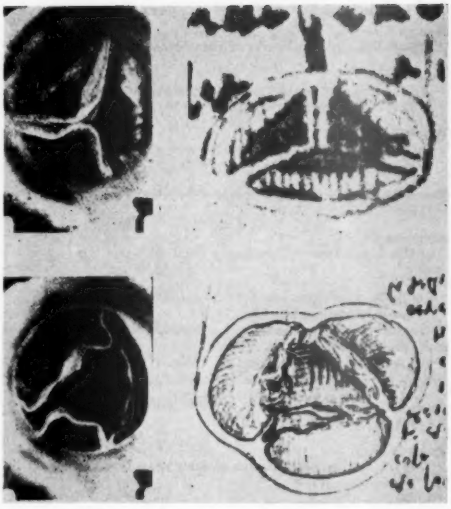

Fig 7 *The aortic valves open and closed. A comparison between the appearances as drawn by Leonardo and cinephotography. Note the dark triangular shadows in the closed cusps, and the wrinkled edges of the open cusps, in both representations.* (*QA IV* 12*r*)

Fig 8 *X-ray studies of jet turbulence, using radio-opaque lucite pellets. Note the reflux component of the movement.* (*Reproduced by kind permission from Dotter & Frische, 1958*)

Another approach to the problem has been made by studies of velocity in the great vessels of human beings. Using a Petôt tube inserted into the pulmonary artery of human beings Jameson (1955) has found an increasing velocity of blood in early systole, followed, he writes, 'by a period of backward flow lasting over 0·1 sec and ending with the completion of the dicrotic notch. The duration and timing of the backward flow suggest that it is associated with retrograde movement and closure of the semilunar cusps'. This statement, made in 1958 comes very close to confirmation of Leonardo's conception.

Complete confirmation, however, can come only through actually seeing the blood flowing through the aortic valve; and this is not beyond the powers of present possibility. However, so far as I know, it has not yet been done. Radiological studies of the turbulence of fluid jets in models, which remind one forcibly of Leonardo's experiments, were made in 1958 by Dotter & Frische, using solid radio-opaque lucite pellets. Like Leonardo they found the movement of a particulate medium necessary to reveal fluid turbulence. One study is remarkable for showing such radio-opaque pellets flowing backwards from a jet of fluid in a manner very reminiscent of Leonardo's hemicycles (Fig 8). The next stage, of course, would be to demonstrate the corresponding turbulence in a human aorta. I am anxious to see this performed.

But the outcome of such verification is really irrelevant to my endeavour to illustrate Leonardo's worthiness to be considered, not only as a master of the visual arts and physical sciences, but of experimental medicine as well. This seems to me to be vindicated by this particular series of experiments. They are all the more astonishing when we realize that they were performed by a man who was ignorant of the circulation of the blood.

But my main motive has been to emphasize a fact which seems too little recognized; that experimental medicine was successfully inaugurated long before the days of Harvey. The three exponents whom we have so briefly considered made this achievement against the intellectual outlook of their times. They worked in a hostile zeitgeist, and therefore could expect no contemporary appreciation of their efforts. This should in all justice be the very reason why their achievements should be highly rated, and not ignored, by historians of to-day.

Erasistratus, I am well aware, is a dim figure. Who among our modern giants of experimental medicine would survive if all his works were lost?

But wherever we catch a glimpse of Erasistratus through the backward mists of time, he appears as an experimental physiologist systematically applying ideas derived from the physics of his day to problems of health and disease in the human body. One has only to read through some of Galen's works to confirm this. Indeed it was just this enthusiasm which aroused the angry Galen in his turn to perform many of his experiments.

Galen's technical brilliance was mostly applied to experiments by ablation; the results of some of them, particularly those on the nervous system, were epoch-making. But the epoch they made did not begin until a century ago when Brown-Séquard, Schiff and others, followed them up.

Leonardo inaugurated physiological experiment by the method of producing models in glass – the *in vitro* method – wherein the conditions of the experiment can be varied under accurate control. He demonstrates perhaps most clearly of them all, the art of creative science, an art which was so evident in the inventive genius of such men as Claude Bernard and Louis Pasteur, in their determination to apply the sciences of physics and chemistry to medicine.

Acknowledgments: The illustrations of the drawings of Leonardo da Vinci from the manuscript at Windsor Castle are reproduced by gracious permission of Her Majesty the Queen.

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Clinical Section

President T C Hunt DM

Meeting February 10 1961
at Paddington General Hospital, London

Cases

Parathyroid Adenoma with Multiple Fibrocystic Changes in Bone and Renal Tubular Calcification

J L Stephen ChM FRCSEd

J A, female, aged 57.

History: The patient presented with a painful swelling just above her right ankle, of three months' duration. Three years previously a giant cell epulis of mandible had been treated by excision and radiotherapy. No history of urinary infection or calculus.

On examination: Rather obese woman. Blood pressure 205/110. Thyroid gland firm and slightly enlarged with a solitary nodule palpable in the upper part of the left lobe. The right tibia presented two tender swellings, one behind the tibial tuberosity, the other expanding the lower end of the tibia. The latter swelling was warm and very tender.

Investigations: Hb 90% Serum Calcium 16·5, inorganic phosphate 2·5 mg%. Alk. phosphatase 54 K–A units. Quantitative tests showed a negative calcium balance.

X-ray of right tibia showed two multilocular cystic areas, the lower one involving the entire width of the tibia and apprently on the point of spontaneous fracture. Similar cystic areas were found in the right femoral neck (Fig 1), pelvis, right humerus and scapula. The hands (Fig 2) showed rarefaction and scalloping of the terminal phalanges, and subperiosteal bone resorption, most marked on the radial side of the middle phalanges. This finding is said to be characteristic of hyperparathyroidism or renal osteodystrophy (Hellström 1954).

X-ray of the kidney area showed tubular calcification but no renal calculi.

Operation: The neck was explored and all four parathyroid glands were identified, confirmed by

Fig 1 *Cystic spaces in right femur*

Fig 2 *Right hand showing scalloping of distal phalanges and subperiosteal resorption on radial side of middle phalanges*

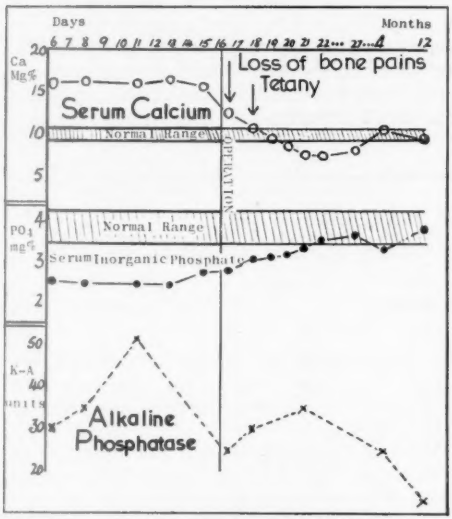

Fig 3 *Serum calcium, phosphate and alkaline phosphatase before and after removal of adenoma*

immediate section. The left upper gland – which proved to be the nodule palpable in the neck – was some 2×1·5 cm in size and was partly imbedded in the thyroid capsule. It was readily freed from the thyroid and proved to be an adenoma composed almost entirely of oxyphil cells.

Recovery was uneventful. The bone pains disappeared immediately after operation. Tetany occurred on the second and third day while the serum calcium was still within normal limits. It responded to the administration of calcium gluconate. The serum calcium and phosphate returned rapidly to normal (Fig 3). Three years later the cystic spaces are almost completely recalcified. The blood pressure and renal calcification, however, are unaltered.

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Hæmosiderosis

M S M Palmer MD (for G Shneerson MD MRCP)

Miss D J, aged 30.

History: First seen at Paddington General Hospital in September 1959. She had had recurrent bouts of hæmoptysis since the age of 10.

On examination: Chest: medium crepitations at the right base. No other abnormal signs detected.

Investigations: Hb 79%. W.B.C. 8,800 (neutros. 80%, lymphos. 20%). E.S.R. 3 mm in one hour (Westergren). Sputum: no tubercle bacilli seen in smears or grown on culture. Moderate growth of *Hæmophilus influenzæ*.

X-rays: Chest showed diffuse mottling throughout the lung fields. Hands and feet normal.

Serum proteins: total 7·6, albumin 3·1, globulin 4·5 g%. Serum calcium 10·9 mg%. Mantoux positive to 1/100. Urine normal.

She was then admitted to the Brompton Hospital for liver biopsy with a provisional diagnosis of ?sarcoidosis ?hæmosiderosis.

Investigations at Brompton Hospital: Pulmonary sufficiency tests: Forced expiratory volume in one second/Forced vital capacity 72%. Diffusion capacity for carbon monoxide at rest 11·0 ml/mm Hg (min. vent. 11·2 litres/min). On exercise 11·6 ml/mm Hg (min. vent. 15·9 litres/min). Indicating moderate impairment of ventilation and gross impairment of diffusion.

Histology: Liver biopsy: no evidence of sarcoidosis. Lung biopsy: many hæmosiderin-laden macrophages within alveoli. Deposits of this pigment in the pleura, interlobular septa and around the small bronchi and vessels. Excess fibrous tissue around the bronchi and small vessels. Diagnosis: Hæmosiderosis.

No cause for the hæmosiderosis was found. Clotting and bleeding time normal, serum bilirubin 0·5 mg%, no evidence of hæmolysis.

Progress: During the two years since these investigations her clinical condition and the radiological appearance have remained unchanged.

Hypogammaglobulinæmia ('Acquired' Adult Form) and Pernicious Anæmia

D D Gibbs BM MRCP & J S Pryor MB (for N Lloyd Rusby DM FRCP)

Mr M H, aged 30.

History: October 1957: developed cough and left-sided pleuritic pain. Referred to the Paddington and Kensington Chest Clinic (Dr J A Keeping), where he was noted to be of poor physique, to have early finger clubbing, and moist sounds were audible in the left lower zone of the chest. Chest X-ray (Fig 1) showed patchy shadowing at both bases, more prominent on the left. He recovered following a course of tetracycline.

February 1958: Relapse with cough, fever, recurrence of pleurisy, and reappearance of basal moist sounds in both lower lobes. He was admitted to St Charles Hospital under Dr Keeping. Initially there was extension of the respiratory infection with right upper lobe consolidation, but resolution of the acute illness followed antibiotic treatment and postural measures. By May 1958 the chest film showed only slight residual shadowing in both lower zones. During this admission he was found to be anæmic (Hb 60%; film – anisocytosis and pale red cells), and he received oral and intramuscular iron preparations. He defaulted from outpatient review when Hb was 70%.

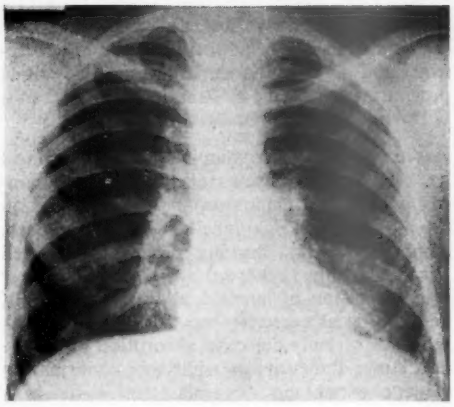

Fig 1 *Chest X-ray 15.10.57*

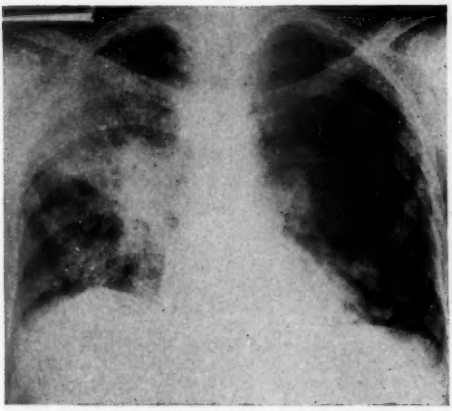

Fig 2 *Chest X-ray 12.6.59*

June 1959: Readmitted to St Charles Hospital. During the preceding six weeks, he had suffered from increasing dyspnœa, cough with purulent sputum, malaise and fever. Chest X-ray (Fig 2) showed further patchy shadowing in both lung fields, and an area of confluent shadowing in the right upper zone. He was seriously ill on admission, but improved rapidly after starting oral tetracycline. He was found to be more anæmic (Hb 58%). Further investigation revealed megaloblastic erythropoiesis, normal fat absorption, and histamine-fast achlorhydria on gastric analysis. A deficiency of serum γ-globulin was shown initially by electrophoresis; a level of 200 mg/100 ml was derived by an immunological method (Gell 1957). In August 1959 he received a parenteral injection of vitamin B_{12} (1,000 μg), as a 'flushing' dose in the performance of a Schilling test. Hb rose to 93%, and a second marrow examination showed normoblastic erythropoiesis.

November 1959: A third admission to hospital became necessary for treatment of a perianal abscess. The serum γ-globulin level had now fallen to 80 mg/100 ml. He was then included in the current M.R.C. clinical trial of γ-globulin for treatment of hypogammaglobulinæmia. Since November 1959 he has received weekly injections of γ-globulin prepared from human pooled serum, given in a planned dosage scheme of 0·025 – 0·05 g/kg body weight/week.

During the past fifteen months his state of health has improved greatly. In July 1960 he contracted a single, comparatively mild respiratory infection, which responded rapidly to an antibiotic; at this time the serum γ-globulin was 240 mg/100 ml.

Past history: Measles and mumps in childhood; neither illness severe. He had not been particularly prone to respiratory or other infections before October 1957.

Family history: None available, an adopted child.

On examination: Poor physique. Height 5 ft 1 in. Weight 105 lb (47·7 kg). Sallow complexion. Tongue normal. Early finger clubbing. Chest clear. Abdomen normal. C.N.S.: No evidence of subacute combined degeneration of the cord.

Investigations: May 1959: Hb 58%. Film: anisocytosis; many cells large and hyperchromatic. P.C.V. 25%. M.C.H.C. 34%. Blood group A Rh+. Sternal marrow (Dr M Hutchings): Hypercellular and megaloblastic; only occasional plasma cells present. Urine: no albumin. Gastric analysis: histamine-fast achlorhydria (histamine 0·5 mg). Stools: occult blood negative. Fat balance normal. Glucose tolerance test normal. Serum vitamin B_{12}: 70 μμg/ml. Barium follow-through: normal small bowel pattern. Schilling test, using ^{60}Co-labelled cyanacobalamin, suggested deficient intrinsic factor.

February 1961: Hb 76%. Film: slight anisocytosis and hypochromia. P.C.V. 39%. M.C.H.C. 28%. W.B.C. 2,700 (neutros. 49%, eosinos. 5%, lymphos. 43%, monos. 3%). E.S.R. 11 mm in one hour (Westergren).

Plasma proteins: Albumin 4, globulin 2g/100ml. Gastric analysis: Histamine-fast achlorhydria (histamine 2 mg). Vitamin A absorption normal.

Gastric biopsy (Fig 3) from high in the body of the stomach: advanced atrophic gastritis shown: plasma cells were absent (Professor I Doniach).

Serum γ-globulin estimations: Serial estimations have been made by Dr J F Soothill, using an immunological method (Gell 1957, Kekwick *et al.* 1961).

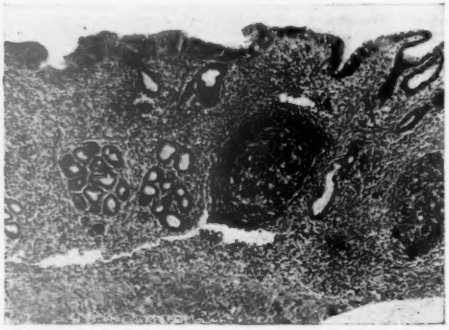

Fig 3 *Gastric biopsy 3.2.61 (Professor I Doniach). The mucosa is thinned and the muscularis mucosæ thickened. Gastric glands are markedly reduced in number and no oxyntic or pepsinogen cells can be recognized. Intestinal metaplasia of much of the surface epithelium and most of the surviving gastric tubules has occurred. The lamina propria is œdematous, rich in capillaries and shows a moderate infiltration with eosinophils, macrophages and fibroblasts. Lymph follicles are abundant, some of them with well-marked germinal centres. Plasma cells are absent.* ×80

Pre-treatment levels	25.6.59	200 mg/100 ml
	6.8.59	160 mg/100 ml
	9.11.59	80 mg/100 ml
	25.11.59	80 mg/100 ml
Levels after starting treatment:	2.12.59	280 mg/100 ml
	3.3.60	480 mg/100 ml
	13.7.60	240 mg/100 ml
	7.11.60	480 mg/100 ml

Discussion: Following Bruton's description (1952), certain patients who show undue susceptibility to bacterial infection have been found to possess very low levels of serum γ-globulin. Recurrent pneumonia is the most common clinical manifestation drawing attention to this condition, and is well illustrated by this patient. The critical level of serum γ-globulin for 'normal' resistance to pyogenic infection is thought to be 0·15–0·20 g/100 ml. The normal range of values for serum γ-globulin in adults is 0·8–1·2 g/100 ml (Gell 1957). Young plasma cells or their precursors are considered to play an important role in antibody production (Sundberg 1955). The dearth of plasma cells in the marrow smear from this patient, and their absence in the gastric mucosal biopsy may be significant.

Unfortunately no inquiry could be made of this patient's relatives. A recessive sex-linked inheritance of hypogammaglobulinæmia has been postulated for affected male children (Porter 1955). By contrast, it has been inferred that 'idiopathic' hypogammaglobulinæmia occurring in adults has been acquired. A pedigree described by Wollheim (1961) suggests that the ætiology of hypogammaglobulinæmia in certain adults may have a genetic basis.

The association of adult hypogammaglobulinæmia and pernicious anæmia has been described previously (Klayman & Brandborg 1955, Lewis & Brown 1957, Crowder *et al.* 1959).

Addendum: A further vitamin B_{12} absorption test has been carried out since this patient was demonstrated (Dr D G Penington). After giving an oral dose of 0·5 μg ^{58}Co-labelled cyanocobalamin, combined with a flushing dose of unlabelled cyanocobalamin (1,000 μg), the twenty-four-hour urine excretion of labelled substance was 0·6% and the fæcal excretion was 88·5%. The result indicates severely defective absorption of cyanocobalamin and provides additional confirmatory evidence of pernicious anæmia.

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Sundberg R D (1955) *Ann. N. Y. Acad. Sci.* **59**, 671
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Multiple Neuropathic Joints ? Syphilitic

R D Green MD MRCP

Mrs A P, aged 74.

History: For twenty years she has noticed increasing stiffness and a fair amount of pain in both shoulders and for the last six to seven years the knees have been affected. Her proximal finger-joints have enlarged but are not painful. Nine months ago when the patient was walking her left leg was heard to snap and it gave way. No real pain was noticed. Her general health is good although she has lost about 1 stone in weight since her accident.

Family history: Father died at 27 – cause unknown. Mother died at 53 in an epileptic fit. Husband died in 1946 from perforated duodenal ulcer. She has one son aged 50.

On examination: The shoulder-joints are extraordinarily mobile and when she attempts to raise her arms the upper end of the humerus can be felt under the clavicle on each side. Proximal finger-joints show gross thickening but movements are fairly free. Knee-joints slightly stiff and grossly distorted in shape. Heart, lungs and abdomen – nothing of note. C.N.S.: No definite abnormality except an extensor plantar response on left.

Investigations: Blood count: Hb 60%; W.B.C. 4,000. Anæmia of iron deficiency type. E.S.R. 13 mm in one hour (Wintrobe). C.S.F. Colourless fluid. Cells: 2 per c.mm. Normal pressure. Protein 20, sugar 59 mg%. Colloidal gold

0011100000. W.R. negative. Blood urea 37 mg%. Serum electrolytes: Na 136, K 4·7, Cl 106, alkali reserve 21·3 mEq/l. Serum calcium 8·8 mg%. Inorganic phosphorus 4·2 mg%.

Biopsy from peri-articular tissue: examination of blood vessels reveals nothing unusual.

X-rays: Hands and knees: considerable disorganization of joints with much osteophyte formation. Shoulders: both humeral heads have been absorbed and there is considerable soft tissue calcification. Appearances are of neuropathic joints. Left tibia and fibula: transverse fractures and evidence of old healed fractures of the fibula (patient has no knowledge of any previous accidents).

Specimen of blood referred to V.D. Reference Laboratory, Whitechapel, gave the following results: Reiter protein complement-fixation test negative. Standard W.R., Price's precipitation reaction centrifuged, cardiolipin W.R. and treponemal immobilization test positive.

Comment: In view of the seroiogical tests it is assumed that this patient's neuropathic joints are due to syphilis, although from their multiplicity and the extensor plantar response syringomyelia might have its advocates. The lack of characteristic sensory changes, however, make this most unlikely.

It has long been held that neuropathic joints result from repeated trauma, not necessarily severe, on insensitive joint surfaces over a long time. Does the present case, with the complete absence of any sensory changes, throw doubt on this conception of neuropathic joint disease? Sharpey-Schafer (1956, *J. Physiol.* 134, 1) and others have demonstrated abnormal baroceptor responses, indicating changes in the autonomic nervous system, in tabes dorsalis but this finding was in tabetics with florid neurological signs of the disease. The present case suggests that other factors, at present unknown, may be concerned with the production of neuropathic joint disease.

Fig 1A *Disorganization of left shoulder due to syringomyelia*

Fig 1B *Disorganization of left elbow-joint due to syringomyelia*

Syringomyelia with Multiple Neuropathic Joints

C A Young FRCP

Mrs H M, aged 76.

History: In early adult life she sustained a painless injury to the left elbow. Thirty-five years ago she scalded and burnt both arms without much pain. For twenty years her left leg has dragged. This leg became weaker in late 1959 and a pathological fracture of the neck of the femur was found on admission.

On examination: Cranial nerves: nystagmus.

Upper limbs: Motor – wasting, weakness, loss of tendon reflexes. Sensation – gross impairment of pain and temperature with relatively normal position, light touch, and vibration sense. Two-point discrimination normal. Joints – Charcot shoulders and left elbow.

Lower limbs: Motor – weakness of an upper motor neuron distribution. Spasticity, left greater than right. Increased tendon reflexes. Extensor plantar responses. Sensation – pain and temperature sense lost in left leg up to L5. Joints – Charcot left hip.

X-rays: see Fig 1A & B.

Comment: A case of syringomyelia with Charcot joints who presented at 75 years of age, having had symptoms for over forty years.

The following cases were also shown:
Hemiballismus
Dr R D Green

Megaloblastic Anæmia due to Epanutin
Dr J Fielding and Dr R D Green

(1) **Scleroderma of Sixteen Years' Duration**
(2) **Scleroderma, Hypertension, Cerebral Hæmorrhage Treated by Evacuation of Hæmatoma**
(3) **Crohn's Disease with Hypergammaglobinæmia**
(4) **Diabetes Mellitus with Retinopathy and Asteroidal Hyalitis**
Dr C A Young

Wegener's Disease
Dr M J McLoughlin (for Dr T A Kemp)

(1) **Pelvic Abscess – ? Crohn's Disease**
(2) **Aortic Aneurysm – Unresected**
(3) **Abdominal Aortic Aneurysm, Resection and Grafting with Plastic Prosthesis Four Years Ago**
Mr H H G Eastcott

Yaws Periostitis
Mr A J Harrold

Dysplasia Epiphysialis Multiplex
Mr M Lawrence (for Mr A J Harrold)

The following specimens were shown:

(1) **Urinary Obstruction** (6 cases)
(2) **The Fœtal Circulation** (2 dissections)
Dr R R Wilson

Books recently presented and placed in the Society's Library

Facing Retirement: a guide to the middle aged and elderly by a country doctor
pp 127 12s 6d
London: Allen & Unwin 1960

Ponten B E
Grafted skin: observations on innervation and other qualities
pp 78
Uppsala: Almqvist & Wilsells 1960

Power Sir D'Arcy
Selected writings, 1877–1930
pp 368
Oxford: Clarendon Press 1931

Prywes M *ed*
Medical and biological research in Israel
pp 562 56s
Jerusalem: Hebrew University 1960

Rawling L B
Landmarks and surface of the human body
3rd ed pp 96
London: Lewis 1908

Relyveld E H
Toxine et antitoxine diphtériques: étude immunologique
pp 164 NF 24
Paris: Hermann 1959

Riches Sir Eric
Modern trends in urology
2nd series pp 287+13 70s
London: Butterworths 1960

Roberts F
Good English for medical writers
pp 179 17s 6d
London: Heinemann 1960

Roesler H
Atlas of cardioroentgenology
pp 124
Springfield, Ill.: Thomas 1940

Rusk H A *ed*
Rehabilitation medicine: a textbook on physical medicine and rehabilitation
pp 572 90s
London: Kimpton 1958

Sarles H & Mercadier M
Les pancréatites chroniques de l'adulte
pp 265 NF 36
Paris: L'Expansion Scientifique Française 1960

Schafer Sir Edward
The essentials of histology: descriptive and practical for the use of students
7th ed pp 507
London &c: Longmans 1907

Sirtori C & Morano E
Il cancro dell'utero dalla macroscopia all'ultrastruttura
pp 268
Milano: Casa Editrice Ambrosiana 1960

Societa Italiana di Radiologia Medica. Comitato per la Protezioni Radiologiche
Norme per le protezioni contro le radiazioni ionazzanti.
pp 260
Milano: Ulrico Hoepli 1956

Solomons B E R
A synopsis of skin diseases
pp 293 30s
Bristol: Wright 1959

(*continued on page 628*)

Section of Orthopædics

President A L Eyre-Brook MS FRCS

Meeting February 7 1961

President's Address

A Bone Tumour Registry – Chondrosarcoma and Fibrosarcoma of Bone.

by A L Eyre-Brook MS FRCS (*Bristol*)

Bone Tumour Registry – Dr E A Codman

The conception of a Bone Tumour Registry was that of the late Dr E A Codman who built up the first such registry in our contemporary civilization. I never met this remarkable man but have always been interested in him since reading his book 'The Shoulder' (1934); but it is not so much the substance of this monograph that continues to make such an appeal, as the preface (which is autobiographical) and the epilogue on 'The Ethics of Advertising by the Medical Profession'. This is surely evidence of an original approach. Codman predicts what has in fact happened: 'Hence a preface, serenely, frankly and even egotistically written by a happy understanding soul might preserve a volume through the centuries although the subject matter might last only a year'. His subject matter has lasted very much longer but the preface will outlive it. He would appear to have been a controversial character, very progressive and energetic. He expresses himself in later years as having regrets at having wasted so much of his time on the opinions of a previous generation and at not realizing that it was the approval of his pupils rather than of his masters that was desirable. A prime object throughout much of his professional life was the spread of what he terms the 'End Result Idea' in hospitals, where there was at that time no knowledge of a follow-up and only a vague impression of the eventual outcome of much of the treatment given. To further this cause he resigned from the staff of the Massachusetts General Hospital, where he was surgeon to out-patients, as a protest against the seniority system of promotion, which was obviously incompatible with the End Result Idea. On the day he heard that his resignation had been accepted, he wrote again, asking to be appointed surgeon-in-chief on the basis of the results of his treatment over the last ten years. The application was accompanied by tabulated results but there were no other series with which to make comparison had any trustee of the hospital so desired. His letter was ignored. He had already started his own hospital with, as he puts it, 'No trustees to consult, no other members of staff to placate if he wished to publish the actual results of the treatment which the patients received'.

It was in 1915, as Chairman of the local medical association, that he organized 'a meeting for the discussion of Hospital efficiency', pursuing his constant aim of forwarding the End Result Idea. Publicity was assured by the presence of the Lord Mayor, but many invited speakers somehow found themselves unfortunately committed to previous appointments. Lest the questions should not be properly posed in his opinion, he relied on a large cartoon to be displayed at the end of the meeting – surely at one of the most dramatic moments of Codman's exciting life. This cartoon is explained in Codman's own words as depicting

'President Lowell standing on the Cambridge Bridge, wondering whether it would be possible for the professors of the Medical School to support themselves on their salaries, if they had no opportunity to practise among the rich people of the Back Bay (the residential portion of Boston). The Back Bay is represented as an ostrich with her head in a pile of sand, devouring humbugs and kicking out her golden eggs blindly to the professors, who show more interest in the golden eggs than they do in Medical Science. On the right is the Massachusetts General Hospital with its board of trustees deliberating as to whether, if they really used the End Result System, she would still be willing to give her golden eggs to support the hospital, and would still employ the members of their staff and thus save the expense of salaries.'

The system of honorary consultant staff was, of course, dependent on the approval and financial support of the members of the staff by the well-to-do residents in the Back Bay district of Boston. The audience were aghast. For weeks his friends

did not speak to him. He was asked to resign as Chairman. He was not reappointed as Instructor in Surgery at Harvard Medical School. His income suffered a severe setback, as is shown in the interesting *curriculum vitae* which appears in this preface (Codman 1934, p. vi).

After this explosion and temporary setback he seems to have maintained constant pressure and slowly gained more and more support for the End Result Idea. The war intervened, with further financial setback, and post-war we find Codman directing more and more of his energy to developing the Bone Tumour Registry, his dream being that in this one disease at least the value of the End Result Idea might be self-evident. The Registry was run from a room given by the Harvard Medical School, which had earlier thought fit to drop him as Instructor in Surgery. He must have gained a vast experience yet he writes, 'I have had the *actual* care of not more than half a dozen cases of this disease' – many consultations, but the patients were *not* handed over to him. And these were free consultations in the America of the 1920s and 1930s, and one is not surprised to read 'The hardest thing in my Quixotic career to explain to my colleagues is my plan of free consultations in cases of bone sarcoma'.

These brief extracts from his preface leave us with an enhanced interest in this remarkable man who did so much to advance the knowledge of bone tumours and of lesions of the shoulder.

Codman's Bone Tumour Registry was manned by clinicians and pathologists – Bloodgood, Coley, Ewing and Mallory – *and*, in a rather smaller way, we similarly recruited on a broad basis. Conceived by a radiotherapist, the late Dr Brian Adams, the Bristol Bone Tumour Registry has been suckled, weaned and reared by our able secretary, Dr C H G Price, in monthly meetings of a panel of three radiologists, three orthopædic surgeons, one general surgeon and one radiotherapist – a group large enough to face up to the six pathologists, who must not have it all their own way!

I would like at this point to express my thanks to the many surgeons who provided the clinical data, and the radiological and pathological material, and who have co-operated so willingly in the follow up, thus enabling the Bristol Bone Tumour Registry to obtain so much material in a relatively short period.

With regard to the *general problem of malignancy and benignity* I cannot but feel some sympathy with Willis (1953): he writes 'Innocence and Malignancy are relative terms of value in the art of prognosis but not denoting distinct species of tumours. The question is not "Is it innocent or malignant?" but "How innocent or malignant is the tumour?" '

In an article on sarcoidosis James (1960) writes: 'Just as the clinical diagnosis remains in doubt without histological confirmation, so does a histological diagnosis remain unacceptable without a consistent clinical picture'. Although written in connexion with sarcoidosis, this is equally valid in bone tumours of cartilage and fibrous tissue and puts a heavier responsibility on the clinician than some clinicians seem to expect.

The following remarks are an analysis of cases registered as chondrosarcoma and fibrosarcoma of bone, and of some kindred lesions which have been accepted as innocent.

Classification

MALIGNANT TUMOURS OF THE SKELETO-FORMATIVE TISSUE

OSTEOGENIC SARCOMA	(1) Osteoblastic (2) Chondroblastic (3) Fibroblastic (4) Parosteal osteoblastic	
CHONDROSARCOMA OF BONE	(1) Peripheral (2) Central	Primary Secondary
FIBROSARCOMA OF BONE		

Osteogenic Sarcoma – Chondroblastic

I must first completely exclude from my detailed survey the chondroblastic osteogenic sarcoma. The *histological* slide of this tumour may show only cartilage and the block may consist almost entirely of cartilage but the *clinical* picture and the *radiology* pronounce the tumour to be an osteogenic sarcoma and the whole specimen would show *ample histological confirmation of osteoid or bone formation by tumour cells – so confirming the tumour as an osteogenic sarcoma.* We have found the chondroblastic osteogenic sarcoma to be the most malignant group of our osteogenic sarcomatous cases. In fact, out of 40 registered cases, there are only 2 remaining in good health, 1 at 6 years, the other at only 16 months.

I do not apologize for showing an example of these osteogenic sarcomata as I cannot illustrate a difference without portraying this lesion, which is not a chondrosarcoma.

Case 1 This man (Fig 1) (B.T.R. 1356) had a tumour deriving from the pelvic girdle, well known as a site for chondrosarcoma, and the histology was that of malignant cartilage, *but* the man was only 24 years of age, had complaints for only two months, and the lesion progressed at a great speed; the condition seven months later is shown in Fig 2. He had succumbed from metastases in a further eight months. This is clearly a clinical picture of chondroblastic osteogenic sarcoma. These tumours usually show denser bony reaction, or more osteosclerosis than do other osteogenic sarcomata.

Fig 1 **Case 1** *Chondroblastic osteogenic sarcoma of right ilium (posterior third) showing osteosclerosis.*

Fig 2 **Case 1** *Chondroblastic osteogenic sarcoma showing gross changes occurring over a period of seven months*

Fig 3A **Case 2** *Chondrosarcoma arising from left superior pubic ramus with pressure atrophy of interior pubic ramus and calcification in the large pelvic tumour*

Fig 3B **Case 2** *Chondrosarcoma of left pubis with cystogram to show elevation of bladder and extension of tumour well over to right side of pelvis*

Fig 3C **Case 2** *Radiograph after hindquarter amputation*

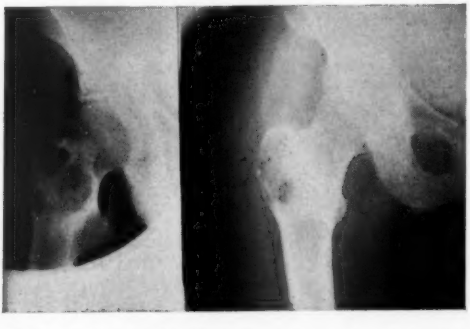


Fig 4 **Case 3** (*Mr A E Jowett's case*). *Debatable cartilage tumour in a man of 60, classified as chondrosarcoma (debatable)*

Fig 5 **Case 4** (*Mr M P McCormack's case*). *Debatable cartilage tumour in girl of 20, classified as chondrosarcoma* (*debatable*)

Fig 6A **Case 5** *Chondrosarcoma probably arising from ala of sacrum and involving ilium and body of 5th lumbar vertebra*

Fig 6B **Case 5** *After excision including all involved bones but not without soiling operative field with friable cartilaginous tumour.* (*Note bismuth injection in left buttock*)

Chondrosarcoma of Bone

Clinical picture: It is difficult to differentiate between chondroma and chondrosarcoma in tumours of the *axial skeleton*, as well as of the *femur*, *humerus* and *tibia* (*the larger long bones*). It is in these bones that we expect to meet chondrosarcoma of bone. With *large* tumours in all these sites, often giving only slight discomfort, we should approach the case with a clinical probability of a degree of malignancy at least. Even in the hand, where the probability can fairly be said to be in favour of benignity, we may find ourselves, in *older* subjects, dealing with lesions showing a considerable tendency to malignancy from its recurrence rate in spite of generous oblations of the affected portion. *Age*, *site* and *size* are of importance in the clinical appraisal. *Pain* is of great importance, but several central chondrosarcomata presented as pathological fractures without preceding symptoms.

Radiology has much to contribute in confirming the size, suggesting the cartilage nature in view of the extensive flaky calcification, and in showing the erosion of the bone of origin. The picture may be conclusive so that one can proceed to definite treatment without a biopsy in such a very large tumour as the following:

Case 2 A woman (B.T.R. 1040) aged 40 who had had one osteochondroma removed from the tibia some years ago and a normal childbirth seven years before the onset of her complaints, presented with a swelling which had only been noted in the last two months (Fig 3A). There were no complaints apart from the lump. The radiograph revealed erosion of the left pubic ramus from which the tumour arose and much calcification in the pelvic mass. The cystogram (Fig 3B) showed the tumour extending right across the pelvis. A hindquarter amputation was performed without previous biopsy (Fig 3C).

Pathology: The *histology* of these cartilage tumours is difficult and our pathologists early recognized that cellularity was no sure guide, the innocent lesion in the finger frequently being more cellular than the malignant lesion in the pelvis.

The features stressed by Lichtenstein & Jaffe (1943) as evidence of malignancy in cartilage are: (1) Many cells with plump nuclei. (2) More than an occasional cell with two such nuclei. (3) Giant cartilage cells with large single or multiple nuclei, or with clumps of chromatin.

Quite apart from the *authority* of the pathological opinion expressed on these sections, we must remember that we are examining a very localized view – a few sections of the biopsy – *samples of a sample*.

Questions such as 'Is this the most ominous area?' and 'Is this a truly representative biopsy?'

Fig 7 **Case 6** (*Mr D M Jones' case*). *Chondrosarcoma of right scapula. No recurrence eight years after excision*

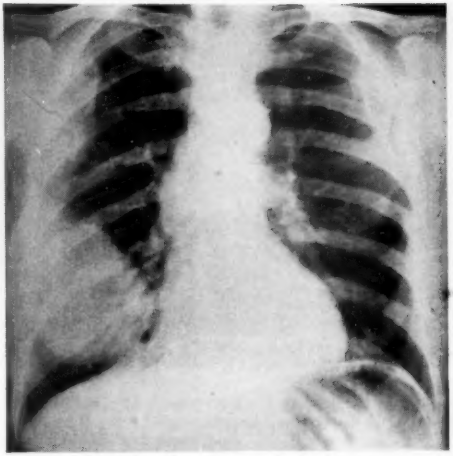


Fig 8 **Case 7** (*Mr R Belsey's case*). *Chondrosarcoma of rib, with short history and death within a year from metastases* →

Fig 11 **Case 10** *Chondrosarcoma in child of 8. Translucent zone with calcification and cortical reaction*

Fig 10A **Case 9** (*Mr R A J Baily's case*). *Central chondrosarcoma of femur showing osteolytic zone with calcification and cortical reaction*

Fig 9 **Case 8** (*Mr G L Alexander's case*). *Chondrosarcoma of twelfth dorsal vertebra – with paraplegia*

Fig 10B **Case 9** *Central chondrosarcoma of left femur showing a thickened and sclerosed supracondylar region, compared with right femur*

Fig 12A

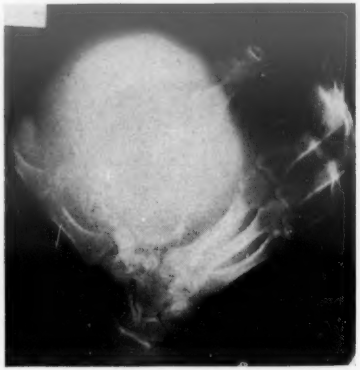


Fig 12B

Fig 12C

Fig 12D

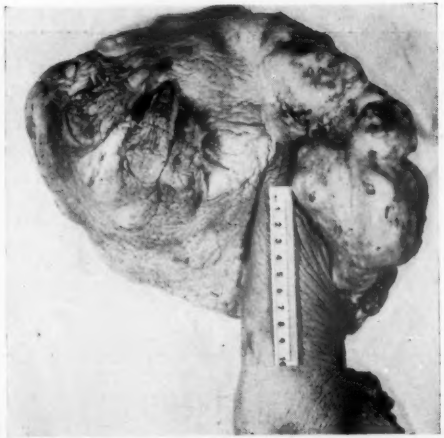


Fig 12E

Fig 12 **Case 11** (*Mr J Bastow's case*). A, *Chondrosarcoma of second metacarpal in woman of* 50. B, *Radiograph of hand.* C, *Recurrence of chondrosarcoma one year after local excision.* D, *Radiograph showing recurrent chondrosarcoma.* E, *Chondrosarcoma. Amputation specimen, three years after second excision, showing immense size of further recurrence.* (*Tumour weighed 4 kg.*) *The patient is alive and well six years later*

Fig 13A **Case 12** (*Mr J Bastow's case*). *Chondrosarcoma of fifth metacarpal in a woman of 55*

Fig 13B **Case 12** *Radiograph of amputation specimen – only the finger and metacarpal were amputated. She is alive and well nine years later*

Fig 14A **Case 16** (*Mr F C Durbin's case*). *Ollier's disease – calcification in cartilaginous masses in femur and ilium*

Fig 14B **Case 16** *Secondary chondrosarcoma in a case of Ollier's disease. The radiograph shows the typical cortical reaction to a chondrosarcoma in the femur and calcification in an enchondroma in the tibia*

Fig 14C **Case 16** *Secondary chondrosarcoma in a case of Ollier's disease. A large soft tissue mass is now seen (one year after Fig 14B)*

are very legitimate in these slow-growing tumours, known gradually to change their behaviour over the years – changes which will be local rather than widespread. Thus the broader panoramic view presented to the clinician and radiologist may in *this* field of bone tumours bring us nearer the truth in many cases.

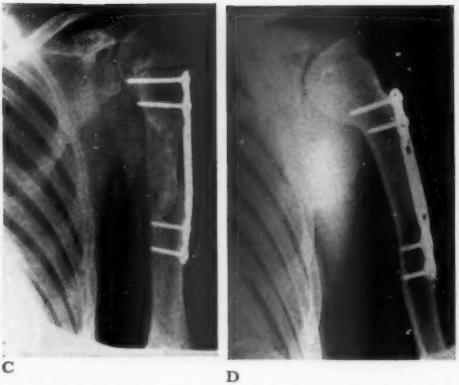
Debatable cases: We have cases which in all honesty, must remain debatable, and the following are the two in our series:

Case 3 A man (B.T.R. 1096) aged 60 had complained of pain in the right hip and buttock, mild, and variable over six years. He then began to complain of increasing pain for the next four months (Fig 4). A biopsy revealed mucoid degeneration in a 'chondroma'. He died of pulmonary embolism within a few weeks. Site, age and pain were clinically alarming features and mucoid degeneration is not a reassuring feature according to Dahlin (1957) but there is little sclerotic bony reaction, even six years later, as is usual in a central chondrosarcoma. The case remains debatable and the death from pulmonary embolism has closed the clinical history.

Case 4 A girl (B.T.R. 1281) aged 20 complaining of recent pain behind the knee. The radiographs (Fig 5) suggested sclerosis round the osteolytic lesion – the pathologists favoured chondrosarcoma but some felt it might be benign. Local excision, and all is well after one year.

In neither of these cases can the diagnosis be stated with assurance.

A B



C D

Fig 15 **Case 17** *(B.T.R. 818)* A, *Large chondroma of humerus treated by block excision and bone graft.* B, *one week after operation.* C, *ten weeks after operation.* D, *twenty-seven months after operation*

Fig 16 **Case 18** (*Mr Hedley W Hall's case*). *Chondroma of radius in a woman of 39, discovered as a result of a pathological fracture. Free from any recurrent trouble seven years after curettage*

Fig 18 **Case 20** (*Mr E S Evans' case*). *Chondromyxoid fibroma of tibia in boy of 12. Free from any recurrence nine years after curettage*

Fig 17 **Case 19** *Calcified chondroma discovered neck of femur. The nature of the lesion was histologically confirmed*

Fig 19 Case 21 (*Mr J F Bourdillon's case*). *Fibrosarcoma of the tibia developing in a woman of 38. An osteolytic lesion with minimal cortical reaction. She survives ten years after amputation*

Fig 21A

Fig 20 Case 22 (*Mr H H Langston's case*). *Fibrosarcoma of the neck of femur in a woman of 50. An osteolytic lesion with some calcification. Slight cortical reaction*

Fig 21B

Fig 21 Case 23 *Fibrosarcoma of the humerus presenting with a pathological fracture in a woman of 54*

Fig 22 Case 24 (*Dr J Lasselter's case*). *Fibrosarcoma of the upper end of humerus showing an osteolytic lesion with calcification and a pathological fracture*

Fig 23 (*B.T.R. 1229*). *A non-osteogenic fibroma in a typical situation in the internal cortex of the lower third of the femur*

Fig 24 *(B.T.R. 1300). A non-osteogenic fibroma in a typical situation in the external cortex of the lower third of the tibia*

Fig 25 **Case 25** *(Mr R A J Baily's case). A fibroma or fibrosarcoma of upper third of the shaft of femur. A very debatable case*

Table 1

Chondrosarcoma cases which have died (14 cases)

No	Age	Site	Symptoms	Survival in years 1 2 3 4 5 6 7 8 9 10	Cause of Death
13	46	Scapula	D A Lump and pain	DXR FQA	Metastases
405	48	Femur L	Ollers Disease Lump	A	Metastases
134	53	Ilium	D A Lump	E E E DXR A	Metastases
744	54	Rib 5th	Pain and swelling	E	Metastases
431	56	Maxilla	Lump in mouth	E E	Other Causes
188	58	Lumbar Spine	Lump and pain	E E DXR E (incomplete)	Neoplasm
1129	59	Dorsal Spine	Paresis	Biopsy	Paraplegia – Neoplastic
1096	60	Femur U	Pain	Biopsy – Post-op death	Pulmonary Embolism
119	61	Scapula	Lump	E E E FQA	Metastases
508	66	Nose	Swelling 4 yrs growth	E E	Neoplasm
804	66	Femur L	Path Fracture	A	Metastases
306	73	Foot	Pain and swelling	A	Other Causes
82	76	Scapula	Lump and pain	DXR	Neoplasm
442	77	Sternum	Lump 11 yrs	E Post operative 6 weeks — Wide excision chest wall	Cardiac Failure

DA = Diaphyseal aclasis
E = Excision
DXR = Radiotherapy
A = Amputation
FQA = Forequarter amputation
HQA = Hindquarter amputation

Clinical material—33 *cases* (*Tables 1 & 2*): Table 1 includes all those who have died. One must note that: (1) The youngest case is 46 years of age. (2) Death from non-neoplastic cause accounts for 4. (3) Of the remaining 10, only 6 died from metastases, 4 from the persisting neoplasm in local recurrence. These 10 cases are all therapeutic failures but long survival has occurred in a number, in 1, five years from the amputation, and in 5 the clinical picture features recurring surgery.

Table 2 shows the survivors; only 3 are under 30 years of age. The survival since the last surgical intervention is:

Ten-year survival	..	3
Nine-year survival	..	4
Eight-year survival	..	2
Five-year survival	..	3
Survival less than five years		7

The Bone Tumour Registry has, itself, only been in existence for fourteen years, which is a limiting factor in survival rate.

One recurrence took place after seven years – as so often in a more malignant form – a cellular fibrosarcoma. The second longest interval before a recurrence was five years, and these 2 cases – among 19 – show the inadequacy of a five-year follow-up as a claim of a cure.

Treatment: Curettage is wholly inadequate for a chondrosarcoma or for a cartilaginous tumour of doubtful innocence in view of age, site, size or symptoms of pain.

As a general guide to the treatment of chondrosarcoma, we cannot do better than follow Dahlin's advice (1957). If the chondrosarcoma is of *low* malignancy, as is so often the case, and is located far enough from the trunk so that a *recurrent* lesion will be operable, one may institute *conservative* treatment such as *excision*, recognizing that few such tumours when they recur will be capable of metastases. Chondrosarcomata of the trunk demand *radical* treatment at the first operation as there is only one good chance in such cases, and I cannot do better than repeat – there is only one good chance.

The hindquarter amputation from the point of view of radical surgery *of the tumour* is often only a very local excision, i.e. pelvic tumours. The smaller pelvic tumours may be dealt with as effectively without the loss of the limb – but the sparing of the vessels and nerves must never be accepted as a justification of a less than radical local excision of these tumours except, of course, in the very elderly.

Table 2

Chondrosarcoma cases which survive (19 cases)

No.	Age	Site	Symptoms	Survival in years
695	8	Tibia U	Pain	A
1281	20	Tibia U	Recent Pain	E
124	29	Ilium	D.A. Lump	E E HQA
1182	32	Femur L	Pain Knee	E A
34	35	Humerus L	Aching and Lump	E E D&R
384	37	Nose	Blocked Nose	E E E
324	38	Ilium	Pain	E
1040	40	Ischium	D.A. Pain in Leg	HQA
478	40	Scapula	Lump	E
477	42	Femur M	2 yrs Pain	A
1142	43	Sacrum	Ache and Lump 3 yrs	E
200	44	Scapula	Lump	E E E
366	46	Ilium	Lump	E
374	50	Metacarpal	Lump	A(F) A(F) A (Arm)
381	55	Metacarpal	Lump 2 yrs Recent growth	A(Fr)
1295	59	Ilium	5 yrs Conserv. Treatment pain in Rt leg	E
1041	65	Rib	Lump 7 yrs Recent growth	E
351	67	Rib	Lump Excisions 20 yrs. and 15 yrs. ago	E
147	74	Humerus U	Path Fracture	E E (Fibrosarcoma)

These tumours have a *dangerously friable surface*, so that portions easily break off and *seed* the wound. It must therefore always be a rule to keep completely outside the tumour throughout the excision and to include any biopsy scar in the extirpated mass. An enveloping layer of normal muscle is a valuable safeguard in such an excision.

The danger of seeding the growth is very great and I have seen a tumour seeded to the bone graft donor site in the ilium, but this was not a cartilage tumour. This merely underlines the need to keep entirely outside the tumour in the definitive excision and to include the whole of the biopsy scar within the excised mass.

Radiotherapy has no place in the treatment of this tumour.

ILLUSTRATIVE CASES

Chondrosarcomata:

Pelvic and shoulder girdle

Case 5 A man (B.T.R. 1295) aged 59 first complained of pain in his right leg and was originally diagnosed as a gummatous lesion. Over the years there was increasing pain and the diagnosis was changed to a tumour, but on radiological grounds the lesion was not thought to be increasing in size; however, one cannot agree with this conclusion. By 1959 he was in great pain, when I first saw him, with absent knee-jerk and sluggish ankle-jerk in right leg (Fig 6A). The tomogram showed the lesion affecting the ilium, ala of sacrum and the body of the 5th lumbar vertebra. The pyelogram showed the right ureter displaced to the left. The tumour was excised, including a third of the 5th lumbar vertebra (Fig 6B) but not without soiling the field by opening into the deeper parts of the tumour and having to withdraw plugs of cartilaginous growth from the intervertebral foramen. This operation could not be called a radical excision. He is comfortable, free from pain and getting about quite well a year later but we must anticipate more trouble. The position would have been different had he been operated on five years earlier.

Case 6 A woman (B.T.R. 478) aged 40 had only noticed a swelling over her scapula in the last month. There was no pain. Radiograph (Fig 7) confirmed suspicions of a chondrosarcoma along the vertebral border and on the posterior surface. The mass was removed *without exposing it*, the line of section being through healthy muscle and normal scapula. This *well-planned* operation has given her immunity from all recurrences in the last *eight years*.

Ribs

Case 7 A woman (B.T.R. 744) aged 55 presented with seven months' complaints of a slowly growing swelling of the chest wall. There was no pain. The tumour was largely intrathoracic (Fig 8). A generous excision was performed but did not prevent the patient dying of metastases within the year.

Dorsal spine

Case 8 A woman (B.T.R. 1129) aged 59 complained of sudden weakness in her right leg. Chondrosarcoma of the 12th dorsal vertebra was suspected in view of the calcification in relation to this vertebra (Fig 9). A laminectomy confirmed the diagnosis but failed to relieve the symptoms. Even in these days of major surgery, the tumour was completely inoperable and she died two and a half years later with complete paraplegia.

The above are mainly examples of peripheral chondrosarcoma although it is not possible in many cases to know whether the tumour is derived from the periphery or centrally. The following, however, are clearly *central chondrosarcomata* affecting the femur and tibia:

Case 9 A man (B.T.R. 1182) aged 32 presented with increasing pain in his knee. Biopsy was performed and was coupled with curettage – a line of treatment which is always inadequate for such a lesion of a major bone. The radiographs (Fig 10A) show the expansion and cortical reaction leading to a broader, denser supracondylar region of the femur. Note the comparison with the other knee – this is typical of central chondrosarcoma (Fig 10B). The pain recurred and the patient accepted amputation a year later.

Case 10 Boy (B.T.R. 695) aged 8. He had had a few weeks' complaint of pain when first seen, the radiograph (Fig 11) showing a translucent zone, some central mottling from calcification, and some surrounding bony reaction – a central chondrosarcoma, not metaphyseal in origin. The pathological opinion was unanimously in favour of chondrosarcoma, which fitted the radiological opinion, although the short history and the age are a little unusual. An amputation has resulted in freedom from any evidence of recurrence locally, or elsewhere, six and a half years later. The only alternative diagnosis is chondroblastic osteogenic sarcoma, but there was no bone or osteoid formation by tumour cells and the tumour is diaphyseal.

Hand

Case 11 A woman (B.T.R. 374) aged 50 complained of a swelling of the 2nd metacarpal (Figs 12A & B) with a fourteen months' history, increasing rather rapidly in size in the last three months. May 1951: Generous excision of finger and metacarpal. May 1952: Local recurrence (Figs 12 C, D); thumb and trapezium were excised. She had a further recurrence and for *nearly two years* she refused amputation. Fig. 12E shows the amputation specimen on 27.10.54. The tumour was $28 \times 26 \times 10$ cm, and weighed 4,186 grams. On all the specimens there was divided opinion among the pathologists as to the evidence of malignancy. She remains alive and well six years after amputation.

Case 12 A woman (B.T.R. 381) aged 55 complained of pain and swelling of the 5th metacarpal after minor injury. There was slow growth in the next three years – more rapidly in the last month (Figs 13A & B). The finger and metacarpal and surrounding soft parts were excised *en bloc* nine years ago. No recurrence. The tumour was $4{\cdot}5 \times 3{\cdot}5 \times 4$ cm, soft and friable and of jelly-like consistency in parts. This tumour remains debatable, with a histological bias towards innocence. The *age* at which it was first noted – over 50 years –

and its recent rapid growth are factors which gave anxiety, but after nine years' survival, all seems well. 'How malignant was this growth?' rather than 'Was it malignant?' is, in my opinion, the correct question.

Secondary Chondrosarcomata

Reference must be made to secondary chondrosarcoma, it being *so important to appraise the risks of harbouring innocent cartilage tumours*, more particularly in the bones of the trunk and in the major long bones.

I have reported 33 cases of chondrosarcomas and among these we find 4 secondary chondrosarcomas arising in cases of diaphyseal aclasis and 1 very unusual case of secondary chondrosarcoma arising in the case of Ollier's disease.

Dahlin (1957) considers it extremely rare for a chondrosarcoma to develop in an enchondroma which was originally clearly benign on critical analysis. Yet Lichtenstein (1959) considers that a chondrosarcoma not uncommonly develops by malignant change in a solitary benign enchondroma, especially of a long bone. It must be very difficult to adduce the origin from a solitary enchondroma which will be silent and undiagnosed until after the malignant change has swept away signs on which a secondary chondrosarcoma can be diagnosed. It may yet be a fair assumption.

Case 13 Man (B.T.R. 13) aged 46 – a clear case of diaphyseal aclasis with many osteochondromas dating from childhood. The chondrosarcoma developed in the right scapula but he would only accept a forequarter amputation three years later and died after a further two years, having developed local recurrences.

Case 14 Woman (B.T.R. 124) aged 29 who developed a chondrosarcoma in the right ilium and, after two attempts at local removal in 1943 and 1944 had been followed by recurrence, a hindquarter amputation was performed with no further trouble in the subsequent twelve-year history. We have radiographs showing an osteochondroma in the neck of the right femur, but there were also tumours on the vertebral borders of the scapulæ to support the diagnosis of secondary chondrosarcoma in a case of diaphyseal aclasis.

Case 15 Man (B.T.R. 134) aged 48 when he first noticed a tumour arising from the pelvis; at operation two years later the diagnosis of chondrosarcoma was confirmed. He died from metastases after a further three years, aged 53. This man had numerous osteochondromata present since childhood.

Case 2, recorded above (B.T.R.1040), had a history of only one osteochondroma on her tibia, the chondrosarcoma arising from her pubis. Her brother had had three osteochondromata removed and her daughter had a typical diaphyseal aclasis affecting three limbs. With this supporting family history I am sure we are quite justified in accepting her as a case of diaphyseal aclasis.

Case 16 A woman (B.T.R. 405) with Ollier's disease developed chondrosarcoma at the age of 48 in the lower end of the femur. She was treated by radiotherapy until amputation was accepted a year later and she died within two years of first presenting herself with symptoms in her leg – a rapid history. She had had an intracranial chondroma removed by Sir Percy Sargent fourteen years previously. Radiographs revealed: (1) Enchondromata with calcification in pelvic bones and right femur (Fig 14A). (2) Areas of translucence and calcification in the lower end of the femur with the *typical cortical reaction* we have learned to associate with a chondrosarcoma in this site (Fig 14B). The tibia shows changes suggestive of calcified enchondromata. A year later the tumour had burst from the bone with a large soft tissue mass on the outer side; this is flecked with calcification as shown in Fig 14C and she died eight months later.

The serious risks which do undoubtedly exist when masses of cartilage survive into adult life thoroughly justify such procedure as block excision and bone graft in bones of the trunk and the major long bones. Even though slight deformity may occasionally result – in Case 17 (Fig 15) it arises from interference with metaphyseal growth – we must be prepared to advise such an operation when large masses of cartilage exist, and, more especially, if there is any suggestion of increasing size after puberty.

Benign Cartilage and Chondroid Tumours of Axial Skeleton and Long Bones

In introducing the subject of chondrosarcoma I felt compelled to paint the picture of chondroblastic osteogenic sarcoma clearly to illustrate the contrast between the two conditions. Now, before closing my remarks on these cartilage tumours of the *trunk* and *long* bones, I feel I should illustrate a few cases of benign chondroma in *these sites*, collected over the same interval as the chondrosarcomata and shown in Table 3. Three were accidental findings in radiographs taken for trauma or mass radiography of chest. One suffered a pathological fracture. One had a twenty-year history of discomfort from interference with movement of the hip, and 4 had minor symptoms. I will also refer to a case of chondromyxoid fibroma, a tumour somewhat alarming in histology but none the less innocent in nature.

Three of the cases occurred in the ribs and it has been said that the chest surgeons have been much more alert to the potentialities of these cartilage tumours and more radical in their approach, consequently with better results. They are admittedly able to be more radical without the serious mutilations which the orthopædic surgeon has only too frequently to advise.

Two cases illustrate the lesions in the long bones:

Table 3
Chondromata of trunk and long tubular bones registered by the Bristol B.T.R. over the same interval as that in which Table 1 and Table 2 were compiled

No.	*Age*	*Site*	*Diagnosis followed*	*Symptoms*	*Follow-up*
CHONDROMA OF BONE					
Treatment—excision or curettage					
153	43	8th rib	Mass radiography	None	11 years
454	39	1st rib	Symptoms	Aching & lump	9 years
623	54	6th rib	Mass radiography	None	7 years
218	84	Sternum	Symptoms	Pain & lump	12 years
568	39	Radius	Pathological fracture	None	5 years
905	56	Femur, upper end	Symptoms	20 years' stiffness of hip	5 years
1405	70	Femur, upper end	Accidental radiographic finding	None	6 months
1206	43	Femur, neck	Symptoms	Pain, stiffness of hip	1 year
CHONDROMYXOID FIBROMA					
709	12	Tibia, upper end	Symptoms	Tender swelling	6 years

Case 18 Woman (B.T.R. 568) aged 39 presenting with a *pathological fracture* of the lower end of the radius in a previously symptomless condition. No cortical reaction was shown in the radiograph (Fig 16). The lesion was curetted six months later, when sound bony union had occurred, the lower end of the ulna being excised on account of the shortening of the radius and to improve the approach to the lesion. She remains free from signs of recurrence seven years after her operation.

Case 19 Woman (B.T.R. 1405) aged 70 with *accidental radiographic findings* of a symptomless calcified lesion discovered after a fracture of the neck of the femur (Fig 17). There is no association between this lesion and the fracture.

No case of benign chondroblastoma was registered during this period, but there was one of *chondromyxoid fibroma* in a boy (Case 20 B.T.R. 709) aged 12 (Fig 18) presenting with complaints of pain and tenderness over the upper end of the tibia. The initial radiograph showed sclerosis around a small translucent area. The lesion was evacuated, but two years later radiographs showed some residual translucence and further evacuation was effected. There have been no signs or symptoms in the last nine years.

Our experience of these tumours is too slight for me to do more than mention this innocent tumour with its slightly sinister histology. The spindle-shaped tumour cells in a fibrous matrix show increasing collagenization with age. There is a chondroid appearance in other portions of the field. Curettage *is* sufficient treatment for this tumour.

Fibrosarcoma of Bone

I propose to record our experience of fibrosarcoma and innocent fibrous tumour of bone. I have excluded secondary fibrosarcoma developing in osteoclastoma and cases diagnosed as malignant synoviomata. Here again I must clearly differentiate between *fibrosarcoma of bone and fibroblastic osteogenic sarcoma.* The marked contrast between the chondroblastic osteogenic sarcoma and the chondrosarcoma in age, duration of symptoms, and in survival is not so evident in the fibrous counterparts in our limited experience. So many fibroblastic osteogenic sarcomata occur in the elderly as a complication of Paget's disease that their average age is near that of fibrosarcoma of bone. The survival in this small group is depressingly short. In view of the relatively minor difference in prognosis, it is clear that in these *malignant fibrous tumours* this differential diagnosis has not the same great importance that we attach to the decision as to whether we are dealing with a chondrosarcoma or a chondroblastic osteogenic sarcoma.

The *radiographs* of a fibrosarcoma of bone usually show a central osteolytic lesion and calcification in part of the tumour is not uncommon (Figs 20 & 22). The *histology* shows *no tumour osteoid* in a lesion composed of malignant fibroblasts.

In 3 cases, the tumour was considered as innocent until the clinical picture clearly indicated otherwise. *Masses of fibrous tissue in bone in middle and old age are always suspect.*

Clinical material: Table 4 shows our 6 cases, the youngest being 38 years of age; the prognosis is grave with 3 out of 6 showing metastases. Two have been too recently treated to warrant any prognostic comment, while only 1 has survived ten years.

Case 21 Woman (B.T.R. 1395) aged 38 presented with *eighteen months' complaints* since an injury: there was aching in the knee, which tended to let her down; there was limited extension. The radiograph (Fig 19) shows an osteolytic lesion without expansion but slight cortical reaction. Yellowish soft tissue was revealed at biopsy. The pathological opinion was fibrosarcoma. The leg was amputated and she survived ten years.

Table 4

Fibrosarcoma of bone (excludiug those developing in osteoclastoma or malignant synovioma)

No	Age	Site	Symptoms	Survival in Years										Cause of death
				1	2	3	4	5	6	7	8	9	10	
1395	38	Tibia U	Pain 18 months Limited Knee Movements	A										
331	50	Femur L	12 months Ache Swelling 4 months	A										Metastases
434	50	Femur U	3 months Pain Limited Hip Movements	DXR		A								Metastases
1338	54	Humerus U	Path Fracture Biopsy and Evacuation	F O E A										
1372	54	Tibia U	Enlarging Lump over 10 years	A										
1258	67	Humerus U	12 months Pain in Shoulder	DXR										Pulmonary Metastases

The following 3 cases were orginally erroneously diagnosed as innocent on material obtained at biopsy:

Case 22 A woman (B.T.R 434) aged 50 complained of *three months' pain* in the hip. Two biopsies in 1950 revealed fibrous tissue of doubtful malignancy. The radiograph is illustrated in Fig 20. She was treated by radiotherapy but amputation took place three years later with excision of the innominate bone six months subsequently. The patient died nearly *six years* after she was first seen.

Case 23 A woman (B.T.R. 1338) aged 54 suffered a *pathological fracture after a fall. No previous complaints.* The radiograph (Fig 21) revealed a suggestion of expansion but no bony reaction. There was a somewhat indefinite edge to the osteolytic lesion at both ends. Biopsy produced a pathology report of benign fibroma. Evacuation by curettage and filling the cavity with iliac bone chips was performed; the main mass of tumour was in part yellow, suggesting xanthomatous change. It seemed to confirm the innocence of the tumour. Three months later there were most alarming progressive clinical and radiographic changes. A further biopsy amply confirmed the tumour as a fibrosarcoma and a forequarter amputation was performed six months ago.

Case 24 A woman (B.T.R. 1258) aged 67 presented with twelve months' aching in the shoulder. The radiograph (Fig 22) shows a translucent lesion with areas of calcification and bone expansion, and a pathological fracture. The histology was thought to confirm a benign lesion. She was, however, treated by deep X-ray, 4,000r over one month. There was remarkable response five months later for an innocent tumour or indeed for a fibrosarcoma. Death from multiple secondaries occurred within three years.

In 3 of these cases, an innocent fibroma was diagnosed initially on the histological section, the clinical picture being the slightly more definite; age, site, pain and response to treatment, although surprising for even a fibrosarcoma, pointing the way to a diagnosis of malignancy.

While it is easy to distinguish between the histology of a typically innocent fibroma and a typically malignant fibrosarcoma, there are many intermediate pictures; again the biopsy may not be wholly representative nor the sections the most ominous in the block.

Treatment: A fibrosarcoma of bone usually calls for amputation, although radiotherapy can be effective and is often the treatment of choice in the upper limb, where the occurrence of bone necrosis and non-union will not destroy the effectiveness of the member.

The prognosis in this small series is more serious than has often been suggested and conservative surgery would appear to have no place in treatment.

Table 5
Cases of fibroma of bone registered during the same interval as the fibrosarcomata of bone in Table 4

FIBROMA OF BONE				
No.	*Age*	*Site*	*Diagnosis followed*	*Symptoms*
216	28	Neck of femur	Symptoms	Pain and limp
1320	53	Upper shaft of femur	Symptoms	Pain for nine months
782	17	Lower shaft of femur	Pathological fracture	None
816	18	Lower shaft of femur (medial)	Symptoms	Pain after trauma
1229	17	Lower shaft of femur (medial)	Radiography after trauma	None
1245	17	Lower shaft of femur (medial)	Symptoms	Pain after football
1300	16	Lower shaft of tibia (lateral)	Radiography after trauma	None
1323	17	Lower shaft of tibia (lateral)	Pathological fracture	None

Benign Fibrous Tumours of Bone (excluding Fibrous Dysplasia)

Finally, to contrast with these malignant lesions of fibrous tissue in an *older age* group, we have the fibromata of the *young* – the non-ossifying fibroma – and we should note how often they are found in very characteristic situations – the inner side of the lower shaft of the femur and the outer side of the lower shaft of the tibia (Table 5, Figs 23 & 24).

Case 25 One of the cases in Table 5 is in a different age group – a woman (B.T.R. 1320) (Fig 25) aged 53 with a history of nine months of pain and an osteolytic lesion in the upper end of the femur with areas of calcification and slight expansion of the bone. All the pathologists were agreed on the innocent nature of the lesion but, as clinicians, we have a suspicious condition in view of the pain and the age, and there must continue to be persisting doubts as to the nature of this lesion. The lesion remains debatable and must be kept under close observation.

In all these tumours consideration must be given to a possible diagnosis of monostotic fibrous dysplasia but in these the histology is usually fairly characteristic.

In these two groups of lesions, the cartilaginous and fibrous tumours of bone, the clinician has a large part to play in an agreed diagnosis and the writing on the wall may be quite as clear to the clinician as to the pathologists. The pathologists naturally request the clinicians to attempt a diagnosis of the *clinical* aspects of the case, including the radiological interpretation, rather than as amateur pathologists, in which field we have such limited experience.

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Section of Ophthalmology

President Sir Benjamin Rycroft OBE FRCS

Meeting February 9 1961

Ocular Symptoms and Signs in Pituitary Tumours

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Mr T Keith Lyle

Reference to any ordinary textbook of neurology or ophthalmology probably shows that one of the early signs of a pituitary tumour is bitemporal hemianopia, which is caused by compression of the optic chiasma, but surely such a field defect cannot seriously be regarded as an early sign? It may also show that primary optic atrophy is another fairly early physical sign. Apart from this being an objectionable term, because the optic atrophy is certainly not a primary affection of the optic nerve but is secondary to compression, be it direct or due to ischæmia by obstruction of the blood vessels supplying the optic chiasma, it can scarcely be regarded as an early phenomenon.

Rarely is reference made to the early subjective ocular symptoms, i.e. the visual symptoms which may prompt the patient to seek medical advice, especially those which may arise in the early stages of compression of the chiasma. This is an unfortunate omission, for in the diagnosis of disease we must first have a patient and usually one with a symptom. Moreover, although other symptoms such as headache and those of endocrine disturbance may be present in the early stages, this is not invariably so, and in any case such symptoms may not sufficiently inconvenience the patient to cause him to seek medical advice. Thus, more often than not, the initial diagnosis of a pituitary tumour depends entirely on the ocular symptoms and signs.

The earlier the diagnosis is made, and the earlier the correct treatment is carried out, the better the prognosis; hence it is vitally important for the clinician to be familiar with the early visual symptoms. It is also important to realize that signs of chiasmal compression, in the absence of symptoms, may be discovered on routine examination of the visual fields.

Pituitary Tumours

As a result of examining the hospital records of a number of cases of pituitary tumour we have been impressed by the fact that defects in the visual fields are usually advanced before they are diagnosed. This is partly due to patients being unaware of their field defects but partly, and substantially, because few opthalmologists are sufficiently 'field-conscious' and many fail to make an adequate examination of the visual fields, even when a patient's complaints indicate that such is desirable. In this connexion Falconer (1946) stated, in relation to the diagnosis of pituitary tumours, 'the important lesson which this study of case histories teaches is that every patient who complains of failing vision for which no adequate cause can be found in the eyeball should have his visual fields carefully tested. This examination is often incomplete, unless it is carried out on a Bjerrum's screen as well as on a perimeter. Only by a complete examination will we recognize many of the cases of pituitary tumour that are at present being overlooked'. He even stated that in the first instance 'probably less than one-fifth of these cases [of pituitary tumour] are diagnosed correctly. This is unfortunate, for in perhaps no other group of intracranial tumours are the results of treatment when carried out in the early stages so gratifying nor in the later stages so forbidding.'

No examination of visual function is complete unless the visual fields are explored. If, however, such examination, as a routine, is a council of perfection only, it should at least be undertaken wherever the history or the subjective examination of the visual acuity suggests that a field defect may be present, or where other symptoms, such as headache or symptoms of endocrine disturbance, might be caused by an intracranial lesion which might involve the visual pathways.

A point which is rarely made in the diagnosis of pituitary tumour is that where the field loss is of the bitemporal non-scotomatous type patients often do not complain of the defect as such, presumably because of its slow, and symmetrical, progress. And when such field defects do give rise to symptoms they may be due to the consequences

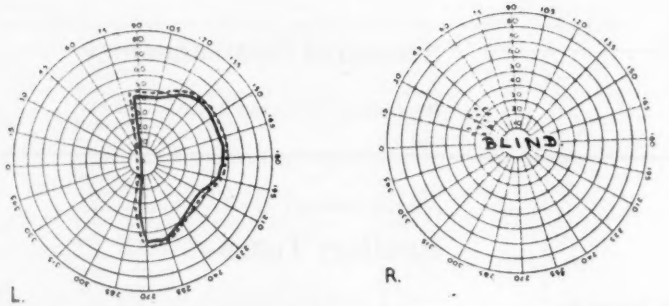


Fig 1 *L.* - - - *=10/330,* —— *=5/330.* *R.* –·–·– = *intermittent to 15/330*

of the defect, e.g. 'a tendency to bump into people' rather than actual complaint of 'loss of side vision'. In fact, in many instances, defective vision is only seriously noticed by the patient when the blind area has become so advanced that it involves the macular portion and causes a defect of visual acuity in one or other eye. On the other hand intelligent questioning of a patient who complains of defective vision may yield information suggestive of a defect in the visual fields.

It is hardly credible that the woman whose visual field defect was as shown in Fig 1, merely complained of a vague difficulty in seeing to get about and difficulty with sewing and reading. It is more incredible still that she was actually seen by more than one ophthalmic practitioner and for some obscure reason had been diagnosed as a case of hysterical amblyopia!

A symptom that sometimes occurs where there is gross bitemporal loss of field is that of occasional diplopia, horizontal in nature, and due to an intermittent and slight divergence of the visual axes, the underlying cause of which (in the presence of a slight degree of exophoria) is, I suggest, the reduction, or in some cases the actual loss, of the area of 'field overlap' common to the two eyes (Fig 2). I have seen 4 patients in whom occasional diplopia was the presenting symptom, the most recent being Case 1.

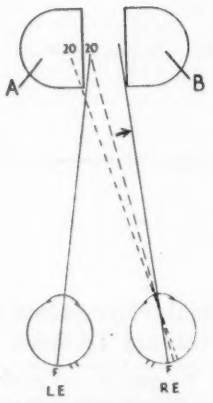


Fig 2 *Diplopia due to divergence of R.E. associated with bitemporal hemianopia.* A *and* B *represent diagrammatically the blind areas in the left and right fields respectively.* F *=fovea*

Case 1 A 38-year-old clergyman whose chief complaint was seeing two rows of lamp posts and two roads side by side when driving his car, especially at night. When reading, he was sometimes aware of seeing 'more letters in a word than there actually were', or 'more numbers (e.g. 20 might look like 2020)'. (Fig 2) He had no complaint relating directly to the field loss and, although he did not complain of headaches, on direct questioning he admitted having had headaches for many years, but they had been worse for the last six months and had sometimes occurred when waking up in the morning.

When he was reading down the test types it was obvious that he had a bitemporal field defect, because he failed to read the letters on the right side of the chart when reading with his right eye and he missed out those on the left side of the chart when reading with his left eye. V.A. 6/9 and N5 in each eye.

Examination of the visual fields showed an almost complete bitemporal hemianopia with the retention of a very small central portion of field common to the two eyes (Fig 3).

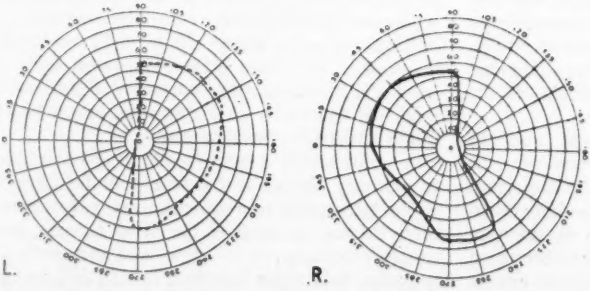


Fig 3 *L. 6/9, N5; 5/330 white.* *R. 6/9, N5; 5/330 white.* *R.+L.* B *=binocular part of total field*

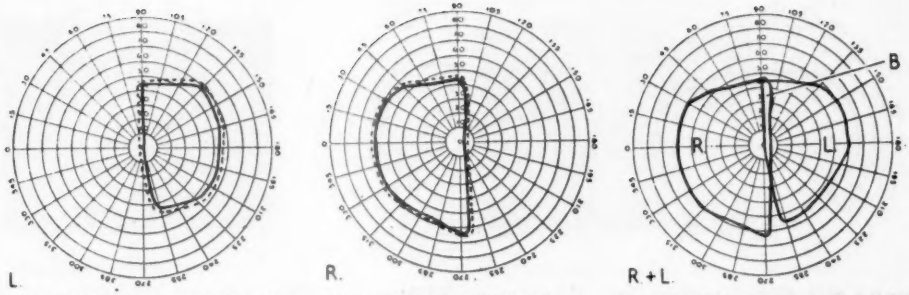


Fig 4 *L. 6/36; 5/330 and 10/330 white. R. 6/9; 5/330 and 10/330 white. R.+L.* B=*binocular part of total field*

Case 2 A man of 24 was referred to Mr S J H Miller as a case of divergent strabismus of the left eye. The patient had first noticed impaired vision of the left eye four years previously. His left eye was turning out at times and he frequently saw double (horizontal diplopia). His visual fields showed an almost complete bitemporal field loss with a gross defect of central visual acuity of the left eye (Fig 4). A large chromophobe adenoma was removed. Some improvement occurred in his visual fields.

In neither of these patients was there any sign of ocular palsy or of any defect of ocular movement.

This so-called 'non-paretic diplopia' associated with defects in both temporal fields has been described by Beckman & Kubie (1929) who stated that three conditions were necessary for its occurrence: a heteronymous field defect, reduction of the acuity at the macula to less than that of the adjacent normal halves of the retinæ, and the power to project the images accurately, the patient attempting to fix eccentrically. Others, notably Chamlin *et al.* (1955) have come to similar conclusions. But the validity of this theory is open to question, for in Case 1, and in other instances also, the central visual acuity of each eye was practically normal.

By contrast, where visual field defects are of the scotomatous type the patient usually presents with the complaint that the vision of one or other eye is defective (unless as rarely happens, both fields are symmetrically affected). Careful examination of the visual fields is essential in order to make a diagnosis of the site of the lesion.

Case 3 Miss B N, aged 21, complained of defective vision in her left eye. She had been referred to an optician who had reported 'Vision R.E. 6/6, L.E. 6/9 partly. A visual field check returned a normal condition'.

On examination, one week later: vision R.E. 6/5 and N5, L.E. 6/60, and N10 unimproved. The direct reaction of the left pupil to light was sluggish as compared with that of the right pupil.

Visual field examination showed a paracentral temporal scotoma in the left central field (Fig 5).

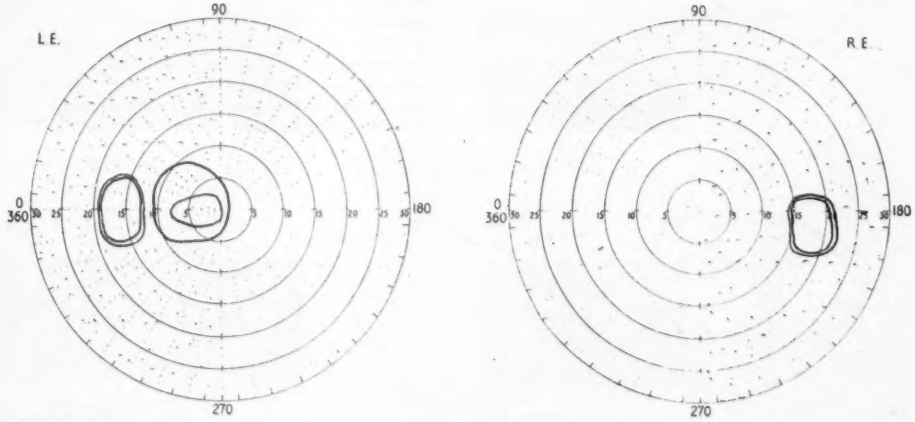


Fig 5 *Miss B N*
L.E. 6/60 and N10 unimproved. White 10/2,000 and 2/2,000; red and green 20/2,000 confused in temporal half of field. L. pupil less active than R. R.E. 6/5 and N5. White 10/2,000 and 2/2,000; red and green 5/2,000, confused in temporal half of field

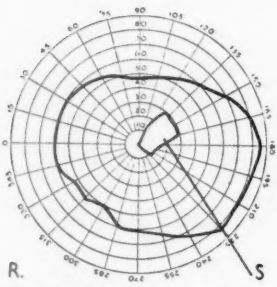
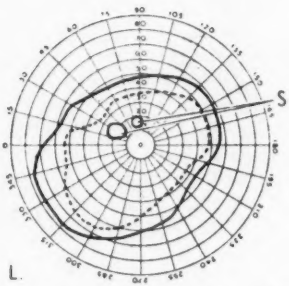


Fig 6 *R. 6/24: 3/330.* S, *scotoma to 5/1,000*



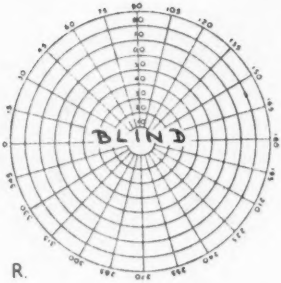
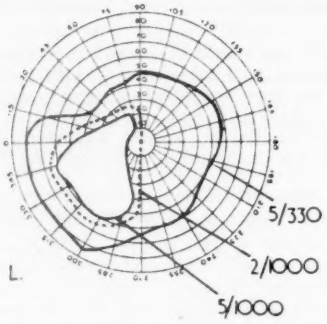


Fig 7 *L.*——*=5/330;* - - - *=2/330.* S, *scotomata to 2/330*

There was no defect in the peripheral field of either eye for white test objects but there was a gross defect for colours in the temporal halves of both fields. This clinical fact left no doubt that there was a chiasmal lesion, in spite of there being no enlargement of the sella on radiological examination. Nor did the encephalogram or the bilateral carotid arteriogram show any abnormality.

At operation Mr Wyllie McKissock found and removed a cyst of the pituitary causing an upward displacement of the left optic nerve. One month later the visual acuity of her left eye had improved to 6/5 and N5, and the scotoma had disappeared.

Case 4 Mr W W, aged 40. A somewhat similar type of paracentral scotoma occurred in this patient who had lost the sight of his right eye, due to what he had been told four years previously was inflammation of the optic nerve. His previous notes recorded that he had had a paracentral upper temporal scotoma in the right visual field (Fig 6) and that, following a negative radiological examination of the skull, a diagnosis of retrobulbar optic neuritis had been made. The sight of the right eye had subsequently gradually deteriorated until it had become blind. When I saw the patient for the first time he was merely complaining of headaches which he had had for the last two years and which were becoming more severe. No visual complaint regarding left eye, V.A. L. 6/5 and N5; right eye quite blind. Right optic disc showed advanced optic atrophy. Left optic disc appeared normal. However, on examination of the left visual field it was obvious that there were (1) two small absolute scotomata in the upper temporal quadrant and (2) a peripheral depression in the upper temporal quadrant (Fig 7). X-ray of the skull showed a gross excavation of the sella and a chromophobe adenoma was removed at operation. The defects in the left visual field subsequently disappeared.



Case 5 Mr H H L, aged 50. In this case also scotomatous defects in the fields were overlooked. The patient had complained of some loss of vision and had several times had his glasses changed without any relief of symptoms. His visual field defect consisted of a bitemporal paracentral scotoma (Fig 8). He had an enlarged sella turcica due to a pituitary tumour. This was satisfactorily treated by radiotherapy, with the complete disappearance of the field defect (Fig 9).

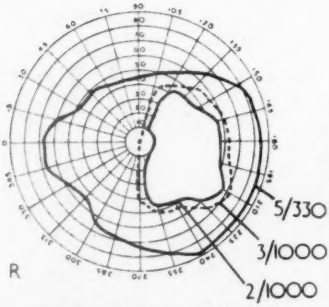


Fig 8 *L. 6/9; J.4. R. 6/36, J.8*

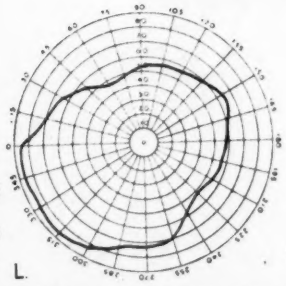
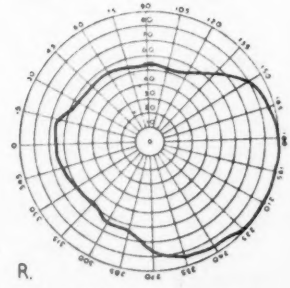


Fig 9 *L. 6/12;* $\bar{c}+0{\cdot}75=6/9$*; add* $\bar{c}+3{\cdot}00$ *=J.2; 5/330, no scotoma*



R. 6/18; $\bar{c}+1{\cdot}00=6/9$*; add* $\bar{c}+3{\cdot}00$ *=J.2; 5/330, no scotoma*

A, *looking straight ahead*

B, *looking up*

C, *looking down*

D, *looking right*

E, *looking left*

Fig 10 *L. III nerve paresis (pituitary tumour).*

A, *looking straight ahead*

B, *looking up*

C, *looking down*

D, *looking right*

E, *looking left*

Fig 11 *L. III nerve paresis (pituitary tumour), post-operative improvement.*

Table 1
Ocular symptoms of visual field defects in pituitary tumour

(1) BITEMPORAL NON-SCOTOMATOUS DEFECTS
(*a*) Patient may be *unaware* of defect *until* the *fixation area is affected*
(*b*) Patient may complain of the *CONSEQUENCES* of the defect: e.g. Bumping into people, knocking things over, difficulty backing a car, difficulty going down steps, etc.
(*c*) Patient may complain of symptoms due to a *defect of binocular vision* caused by *reduction* of *area of field overlap* in central part of the binocular field: e.g. difficulty in focusing, difficulty in judging position and distance, diplopia.
(2) SCOTOMATOUS DEFECT (usually unilateral at first) Defective vision noticed

Table 1 is an attempt to classify the ocular symptoms caused by visual field defects in pituitary tumours.

Ocular palsy, especially of the III cerebral nerve, may sometimes be caused by the lateral expansion of a pituitary tumour, and in some cases, the resulting diplopia may be the presenting symptom, as in Case 6.

Case 6 Miss B P, aged 48, for several weeks had had double vision of a horizontal type when looking to the right, and also pain around the left eye. She had a partial left III cerebral nerve palsy with slight left ptosis and defective adduction, and some defect of elevation and depression (and slight intorsion on depression) (Fig 10). There also appeared to be a lesion of the left ocular sympathetic, because the left pupil was slightly smaller than the right. No defect in visual fields.

Although the sella turcica was of normal size, radiological examination of the skull showed erosion of the inferior aspect of the lesser wing of the sphenoid and erosion of the left anterior clinoid process and floor of the left optic canal. A left carotid arteriogram showed no abnormality. Mr Murray Falconer, to whom I referred this case, thought that in view of the normal arteriogram there was probably a lateral extension of a chromophobe pituitary adenoma. This proved to be correct. After operation there was considerable improvement in her eye movements (Fig 11).

Mr Clover will present some facts about the visual symptoms and signs in a series of cases of pituitary tumour, seen and treated at the National Hospital, Queen Square, and some at King's College Hospital. For permission to refer to these cases we are indebted to the physicians and surgeons at the National Hospital, and especially to Dr S P Meadows, Mr Harvey Jackson and Mr Wyllie McKissock. Also Mr Murray Falconer of the Guy's Maudsley Neurosurgical Unit to whom our cases were referred from King's College Hospital.

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Mr Peter Clover

The clinical records of 100 cases of proven pituitary tumour have been examined. They are the records of patients who have been submitted to operation at the National Hospital, with the exception of 4 which were referred from King's College Hospital to Mr Murray Falconer at the Neurosurgical unit of the Maudsley Hospital. Some, but not all, of these patients we have seen ourselves.

The notes were obtained in a consecutive series from the Hospital files, and were rejected only if no histological examination of the tumour had been made. This mode of selection avoids a tendency to an unduly high incidence of ocular symptoms which might be expected if the cases had all been collected from the ophthalmic departments. On the other hand, since marked visual defect is one of the most important indications for surgery in patients with pituitary tumours it would be surprising if there were not a very high proportion of such defects in this series.

Chamlin *et al.* (1955) studied a large number of patients with pituitary tumours, including in the series cases in which a firm clinical diagnosis had been made, though not necessarily a histological examination. Comparison with this series shows that the results of our analysis are very similar.

The histological classification of our cases was as follows: 74 chromophobe adenomata, 20 mixed cell adenomata, 6 eosinophil adenomata.

Fig 1 shows the age incidence of the onset of the illness from the patient's point of view. It is apparent that the onset of symptoms occurs most often at an age when presbyopic changes would be expected. The early signs of pituitary tumour are often misinterpreted as those of presbyopia. 56 of the patients were men, and 44 women.

Endocrine and metabolic changes may long precede other symptoms (Jefferson 1957) but perhaps partly because of their insidious onset and long duration, and partly because they do not cause much inconvenience, they are not as a rule the symptoms which the patient regards as marking the beginning of his illness, or which cause him to seek help.

Table 1 shows the symptoms which first caused the patient to see a doctor. In 94 of these cases the symptoms were such that the patient would probably go or be referred to an ophthalmologist, or more likely an optician.

Table 2 shows the *first* symptoms noticed by the patient; that is, those that were regarded by him as the start of his malady. Note that there is a large preponderance of symptoms which suggest an ocular origin. Clearly it is to those engaged in the examination of the patient's sight that the first opportunity for diagnosis is usually offered.

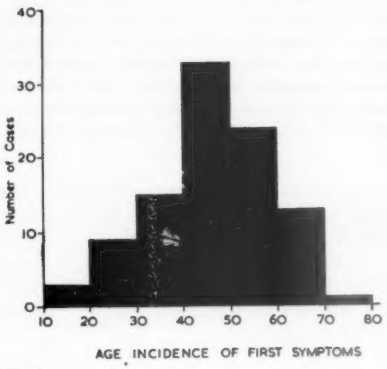

Fig 1

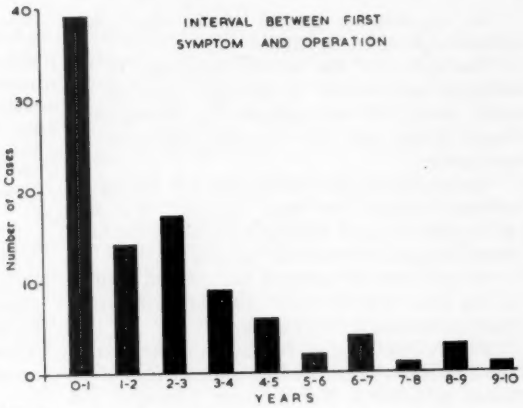

Fig 2

Table 1
The nature of the presenting symptoms

71	Purely ocular
11	Ocular symptoms and headache
8	Headache alone
1	Dementia and visual defect
1	Diplopia and pain
1	Visual defect, headache, diplopia and fatigue
2	Attacks of loss of consciousness
1	Admitted in coma
1	Vomiting and headache
1	Headache and pain around the eye
1	Fatigue. Loss of libido and acromegalic changes
1	Incidental finding during treatment for obstructed bowel

Table 2
Nature of the symptoms considered by the patient to be the first

72	Purely ocular
8	Ocular and headache
9	Headache only
1	Visual defect and dementia
1	Visual defect and pain around the eye
1	Visual defect and amenorrhœa
1	Visual defect and attacks of loss of consciousness
1	Headache and pain around the eye
1	Vomiting and nausea
3	Fatigue and sexual dysfunction
1	Acromegaly and headache

Fig 2 shows the interval between the onset of symptoms and operation. This is not the same as the interval between the onset of symptoms and diagnosis, for surgical treatment may be deliberately delayed for medical or domestic reasons; or it may be due to fear, or due to neglect on the patient's part. One of the patients in this series waited for ten years before consenting to operation; another young man who had a bitemporal hemianopia when he was first seen at another hospital failed to reattend for nine years. But in many cases the delay was due to incorrect diagnosis at the patient's first visit.

Table 3
Initial diagnosis made in 30 cases

14	Refractive error
1	Myopia
1	Astigmatism
1	Amblyopia
1	Tobacco amblyopia
2	Optic neuritis
2	Glaucoma
2	Hæmorrhage behind the eye
2	Migraine
2	Optic atrophy (? 'and therefore no treatment available')
2	Reassured

Table 4
Analysis of the field defects

79%	Hemianopic type of defect, affecting the periphery of the field
15%	Paracentral hemianopic scotoma; periphery of field not affected
1%	Arcuate type of defect
2%	Unilateral central scotoma indicating optic nerve compression
2%	Testing impossible
1%	No field defect demonstrated

Two of these cases showed homonymous visual field defects; in 9 defects were found by the quantitative use of red targets and in 4 these were the only visual field defects to be found

Table 3 shows the initial diagnoses made in 30 cases. (These were the only cases in which the initial diagnosis was recorded.)

Visual Field Defects

Undoubtedly the ocular signs of greatest importance to the ophthalmologist are the visual field defects. These were present in all but 3 of our cases, and 1 of these patients was not conscious at examination. However, it has to be remembered that these patients were all candidates for operation.

An approximate analysis of the visual field defects is presented in Table 4.

The spread of the tumour may lead to the selective involvement of the optic tract or the optic nerve, and this accounts for the homonymous defects and the unilateral scotomata respectively.

The frequency with which resort to the use of coloured targets has been rewarded is noted. In 4 cases no visual field defect at all would have been demonstrated without their use.

At least 6 of our patients had noticed nothing wrong at all until the defect was demonstrated to them on routine testing for glasses.

Twenty-eight were conscious of the existence of some disability because of the consequences of the visual field defect. For instance 3 patients had noticed that they failed to see the ball in certain positions while playing tennis; a barmaid found that she could not see the bottles which stood on the left of the one she was regarding; a motorist failed to see a cyclist approaching from his right, and nearly collided with him. Many first appreciated a defect in the vision of one eye when the other was temporarily shut because of a subtarsal foreign body.

The consequences may, however, be less obvious; a patient with an homonymous scotoma noticed that when reading she frequently lost the right line; several patients suffered from non-paretic diplopia which has already been mentioned by Mr Lyle. Many of the remainder were conscious of the visual field defect as such. They noticed a sensation of looking through dirty glass, or through mist in the affected region of the visual field.

An insidious onset and a slow unremitting progression of the defect is not invariable. In 4 of our cases the onset was sudden. One patient noticed a scotoma on waking, another noticed its sudden appearance whilst out walking; one girl found the visual acuity reduced within four days to the ability to perceive light.

In 1915 Cushing & Walker had noted the occurrence 'of periods of lowered visual acuity and contracted peripheral field from which recovery occurred followed by the failure of vision later', and attributed these to changes in the tension of the growth due to œdema or increased vascularity. Four of our cases were noted as showing spontaneous improvement of vision of this sort. Another 4 cases showed sudden deterioration of visual field defects which followed attacks of severe headache. (Two of the cases showed the other signs of pituitary apoplexy.)

MF (a patient not included in this series), a woman of 37, had noticed a film over the right side of her vision for three weeks. She attended an optician's shop where the refractionist was unable to improve her visual acuity beyond 6/12 in each eye, and she was referred to Mr R P Crick at the Royal Eye Hospital. Here she gave a further history that five years previously, immediately after the birth of her last child, the sight in the left eye was very poor for a few hours but recovered within the day. Examination of the visual fields showed bitemporal hemianopic scotomata, and subsequently the presence of a chromophobe adenoma was confirmed.

This case shows not only the transience of the field defect, but its occurrence in association with the patient's pregnancy and delivery. These rapid changes in field defects may be held to support a mistaken diagnosis of optic neuritis, especially where the field defect is unilateral, or its bilateral nature is not appreciated.

Ophthalmoscopic Changes

The most important ophthalmoscopic change is pathological pallor of the disc which was recorded in 56% of cases; there is little doubt that this is a generous estimate. The absence of this change is a finding which cannot carry much weight in excluding the presence of a pituitary tumour.

Other changes at the nerve head: One disc was noted as swollen with indistinct edges. Another case showed a thrombosis of the inferior temporal vein. A third showed an attenuated branch of the superior temporal retinal artery. These last two changes distracted attention from the signs of pituitary tumour for some months.

Diplopia

Diplopia was recorded in 20 cases. Those classified as 'non-paretic diplopia' are those in which no impairment of the actions of the extrinsic ocular muscles was demonstrated clinically, or could be deduced from the history.

Diplopia was thought to be paretic in 5 patients, doubtful in 2 and non-paretic in 13.

Two of the paretic cases occurred in attacks of pituitary apoplexy. One of these showed a complete right ophthalmoplegia and a left VI nerve palsy, and the other a partial III nerve palsy. Two of the remaining cases showed partial III and IV nerve lesions, and the other case a VI nerve lesion.

Changes in the Reaction of the Pupils

These occurred in 20 cases. In 18 patients they were attributable to the visual field defect. Of the remainder, one was abnormal because of a previous inflammatory disease; the other showed absent reaction to light, and a slightly impaired reaction to convergence. Later this patient developed an homonymous scotoma. This is mentioned because similar cases have been reported by Moore (1925), LeFever (1935) and Chamlin *et al.* (1955) in association with

tumours in the region of the third ventricle. *Headache* is not strictly an ocular symptom, but it comes within the ophthalmologist's purview. In this series it was absent in 53 patients. It is worth noting that in only 2 of those cases in which it did occur did the nature of the headache suggest an ocular origin.

Pains and Aching Round the Eye

Thirteen patients complained of this symptom. Two at least were clearly due to neuralgia of the V cerebral nerve.

An examination of the reports on the radiological examination of the skull showed that in four of these cases no abnormality was present.

The material available did not permit an accurate assessment of the changes in visual acuity in patients with pituitary tumours.

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The Treatment of Pituitary Tumours

by Joe Pennybacker FRCS (*Oxford*)

The ophthalmologist's concern with pituitary tumours is largely confined to the two types which cause visual symptoms, namely the chromophobe and chromophil adenomata. Both types, by erupting upwards from the sella, can compress the optic nerves and chiasma and cause the characteristic field defects and loss of acuity which have been described. Visual symptoms are the surgeon's chief concern too, because failure of vision is the common indication for surgical treatment of these tumours.

We speak of chromophobe and chromophil adenomata because generally the predominant cell type of the the tumour produces a characteristic clinical picture. The chromophil tumours cause acromegaly in greater or less degree and the chromophobe tumours produce varying degrees of hypopituitarism; loss of body hair, amenorrhœa, impotence, lack of energy, &c. But this is not always so: sometimes a chromophobe tumour will cause enlargement of the sella and a chiasmal lesion with no symptoms or signs of hypopituitarism. And sometimes there is a mixture of the features of acromegaly and hypopituitarism, and in these the tumour is best described as a mixed cell adenoma.

Most pituitary tumours grow very slowly. It is common knowledge, for instance, how easily acromegaly can slip up on one, unnoticed by the patient or those who see him every day. I saw a doctor recently whom I had not seen for about twenty years. I remembered him as a rather heavy-featured young man, but he is now a well-marked acromegalic. He has no symptoms and the change in his appearance has been so gradual that his family and his partner had not noticed it. I have no doubt that he has had a chromophil tumour for at least twenty years, and even after that time it has done nothing more than produce a very gradual alteration in his appearance. Similarly, it is very common to see a middle-aged person with a chromophobe adenoma who on enquiry will be found to have symptoms of hypopituitarism dating back to adolescence or early adult life. In some cases, the length of the history is such that we may be misled into thinking that we are dealing with a congenital tumour such as a craniopharyngioma. Or indeed we might wonder whether pituitary adenomata are themselves congenital tumours.

Not all pituitary tumours grow so slowly of course. There are some which grow very rapidly and recur quickly after operation. Some of these are carcinomata, and they have distinctive histological features. Some adenomata develop cysts, and others are prone to hæmorrhage, both processes leading to a rapid expansion of the tumour.

Another feature which interests me is the difference in the growth pattern of chromophobe and chromophil adenomata in relation to the sella turcica, and the optic nerves and chiasma. The chromophobe tumours expand the sella and project upwards to compress the optic nerves and chiasma very readily, but the chromophobe tumours may produce gross enlargement of the sella without any visual disturbance at all. The fact of the chromophil tumour being confined within the sella is, I think, responsible for a common symptom in acromegaly, namely severe bitemporal headache. This can be very distressing at times, and one acromegalic (R.I. 7976/43) was admitted as an emergency because of it. It had come on two or three days after a dental extraction, and he was obviously in very severe pain when he came into hospital. He described it as a hammering between the temples, and there was a good deal of vomiting. There was no field defect or loss of acuity, the fundi were normal, as was the spinal fluid pressure, and so we assumed that the headache was not due to increased intracranial pressure. This kind of bitemporal headache in acromegaly usually responds dramatically to X-ray treatment, but while we were arranging for this, the headache suddenly ceased. I saw him about an hour later and found a well man, obviously relieved, but he noticed that something had happened to his vision and he now had a defect in both temporal fields. It would seem likely that the tumour had ruptured through the dia-

phragma sella and thus 'decompressed' itself. This patient has been kept under regular observation and he has remained well during the past eighteen years. He leads an active life as a farmer, the bitemporal defect has not progressed and the visual acuity is normal.

This case demonstrates another feature of acromegaly which is worth noting. When a chromophobe tumour produces visual symptoms, these are usually progressive and will go on to blindness unless they are relieved. Many acromegalics, however, have no visual symptoms, and those who do develop field defects may remain stationary for many years, and it is uncommon for them to progress to serious impairment of vision. This accounts for the fact that out of 171 cases of pituitary tumour verified at operation in Oxford, there have only been 6 cases of acromegaly, whereas there were 65 cases of acromegaly which did not require operation.

The operation for pituitary tumours is an incomplete one, directed primarily to relieving pressure on the optic nerves and chiasma. The tumour is usually approached by the sub-frontal route, the capsule is incised and the interior sucked out, curetted or removed with rongeurs. This intracapsular removal reduces the bulk of the tumour and the upper part of the capsule can then be pulled down from above to free the chiasma, and from both sides to free the optic nerves. But there is tumour left and it will recur in time like any other tumour which is not completely removed. It is because of this that radiation treatment of the remnant has been a common practice for many years, and there is no longer any doubt about its value. Indeed many regard these tumours as so highly radiosensitive that they should be given this kind of treatment before surgery is considered. At the Lahey Clinic in Boston, I believe only about 12% of pituitary tumours find their way to the operating room: the others are all treated by radiation. Being somewhat conservative in the use of the knife and the shedding of blood, I must say that this approach appeals to me: if one can spare a person a major operation on his head and do as much for him with another method of treatment which carries no risk, this is obviously all to the good.

When the surgeon sees a patient with a pituitary tumour, the first decision is usually as to whether or not his symptoms demand treatment, and if so, whether operation or radiation treatment should be advised. There is no doubt that we see these patients earlier than we used to do, I suppose because the country is being populated by bright young doctors who make the diagnosis at a stage when it really depends on an X-ray of the sella. Although the majority of cases still come from the ophthalmologists, there are many from the physicians and gynæcologists who have patients sent to them suffering from anæmia, lack of energy, amenorrhœa, &c. They all have a large sella, most have some field defect of which they might not be aware, and a few have no visual defect at all. Not long ago, I saw 3 patients with pituitary adenomata at a single outpatient clinic. One had come from a physician, 1 from a gynæcologist and 1 from a general practitioner. Each had only an upper temporal defect in one field, and all had normal acuity. For these I would recommend radiation treatment *with the provision that a close watch can be kept on the fields and acuity during the treatment*. We see these patients at weekly intervals, and they are told to report at once if they notice any significant change in their vision during the intervals. This is because radiation is thought sometimes to cause a temporary swelling of the tumour, and if a nerve is already much compressed, further swelling might cause irreparable damage, but I have not known this to happen in any of the cases which we have had under observation.

The clinical effects of radiation treatment are usually quite definite.

March 1958: A woman aged 57 (R.I. 183130), with a considerable hypertension (200/120) and an enlarged sella, she was one of the group who had been devoid of body hair throughout her life, despite which she had borne 4 children. There was a complete hemianopia in the left eye, and a small notch in the upper temporal field on the right side, V.A. was 6/36, J.16 left, and 6/12, J.6 right. Knowing that she had high blood pressure, she was anxious to avoid operation, so she was given a course of radiation treatment. By October 1958 the acuity was 6/18, J.6 left, and 6/9, J.2 right. There was still an upper quadrant defect in each field, but by February 1961 the fields were full to a 5 mm white object. There was still a relative upper quadrant defect to red objects in the left eye.

The gross effects of radiation treatment, i.e. in reducing the bulk of the tumour, can be seen by air-encephalography. Indeed, these effects may sometimes be more than we have bargained for, as within the past six months we have had 2 patients with large pituitary tumours treated by operation and radiation who have done well as regards vision, but have developed cerebrospinal rhinorrhœa. Both have had attacks of meningitis. One we have explored and found no evidence of tumour at all. The other is in hospital at present recovering from meningitis, but an air-encephalogram shows that the tumour has shrivelled up. Presumably in both cases, the tumour has eroded the sphenoid or posterior ethmoid air cells, and as it shrivelled after radiation treatment, its plugging effect ceased. Such fistulæ have to be closed, and this can be a difficult technical problem.

There are at least two groups of tumours which

do not respond satisfactorily to radiation and these are the cystic ones and those in which a hæmorrhage has occurred. It may be impossible to identify these changes on clinical grounds, but if there is a story of a rapid or sudden loss of vision, with headache, vomiting, and pain behind the eyes, such cases usually demand operation, and promptly. The following is a case in point.

F S, female aged 60 (R.I. 278112/59); admitted 20.8.59. She had had mild symptoms of hypopituitarism for about two years and for six months had thought that her sight was failing. Ten days before admission, on returning from watching a tennis match, she developed a severe headache which she described as being behind the eyes. This persisted and she vomited frequently, and her sight became misty. She was admitted to another hospital where it was found that she had a bitemporal hemianopia and an enlarged sella. The spinal fluid was clear and colourless and the pressure was normal. When she was transferred to the Radcliffe Infirmary, the headache had largely abated, leaving her with a feeling of pressure behind the eyes. The bitemporal defect was confirmed, and V.A. was 6/36, J.16 in each eye. At operation, there was a tense bluish tumour projecting upwards from the sella. Nothing could be obtained on aspiration with a needle, but when the capsule was incised, dark tarry blood escaped and about 8 ml of this was collected. The interior of the tumour was curetted, and the accessible portion of the capsule excised. She improved rapidly and had a course of radiation treatment after operation, and twelve months later she regarded her general health and eyesight as normal. The acuity was 6/9, J.1 in each eye, but although the peripheral fields were full, there was still a bitemporal defect to small objects on the Bjerrum's screen.

The result of treatment, whether surgery or radiotherapy or a combination of both, depends to a large extent on how long the visual pathway has been subjected to pressure. The most dramatic response occurs in those cases of rapid loss of vision in which an operation such as I have described may bring about a full recovery of the fields and acuity, often within a few days. On the other hand, if there is bilateral optic atrophy and a long-standing field defect, operation may do little more than prevent further loss, but even this may be very valuable in preventing complete blindness.

There have been two or three important advances in the management of these tumours. Hormone therapy has undoubtedly given the surgeon a good deal more leeway: in the old days we were always afraid to remove too much of the tumour, because some of these patients made good visual recoveries but were left as pituitary wrecks. There is no doubt that hormones have made the operation and the post-operative period less harrowing, and they are highly effective in the treatment of the general symptoms of hypopituitarism. Of only slightly less value to the surgeon is the introduction of intravenous urea for the reduction of intracranial pressure. This substance shrinks the brain to such an extent that exposure of these tumours is usually quite easy. A third minor technical advance is the small craniotomy: a small bone flap gives all the room that one can use, and there is less risk of complications such as hæmatomata. As I see it now, the surgery of pituitary tumours is safer than it has ever been, and in radiation therapy we have another method, the safety and relative value of which we have yet to establish. And as operation may be called for at any time, I think it important that the neurosurgeon be asked to see these patients as soon as the diagnosis is made.

The Endocrinology of Pituitary Tumours

by E J Ross MD MRCP (*London*)

Tumours in the region of the pituitary are of interest to ophthalmologists because of their local effects to the fibres of the optic chiasma. Their endocrine interest and importance lies in the local damage caused by their presence to the various parts of the pituitary gland and its functionally related areas in the hypothalamus. In its capacity as the master gland, failure of pituitary function secondarily affects the secretion of other endocrine glands of the body, in particular, the gonads, adrenal cortex and thyroid.

The local effect of an expanding tumour within the sella turcica is failure of production of trophic hormones. The clinical effects of failure of these pituitary hormones is typically manifested in a characteristic sequence. It has been shown experimentally (Ganong & Hume 1956) that when varying amounts of pituitary tissue were removed from dogs, gonadal function was the first to be depressed, then thyroid, and finally adrenocortical depression was seen. This sequence of selective failure of end-organs is seen in many cases clinically (Hubble 1952, Nurnberger & Korey 1953); in others signs and symptoms of adrenal insufficiency are noted before those of hypothyroidism (Mogensen 1957). In all cases, however, the cells or perhaps the enzymes which are most sensitive to destruction by pressure are those responsible for the production of gonadotrophins. The result is the cessation of menstruation or impotence, decreased growth of beard and loss of pubic and axillary hair which may precede other symptoms and signs of the presence of a pituitary tumour by many years. The loss of body hair is in part also due to loss of adrenal androgens. Scalp hair retains its previous rate of growth.

Either thyroid or adrenal hypofunction may be the next to appear. Clinically symptoms of

thyroid hypofunction may be present such as cold intolerance, lethargy and mental apathy whilst no symptoms referable to adrenal insufficiency may be apparent. However, if laboratory tests of function of thyroid and adrenals are performed it is usually found that evidence of adrenal hypofunction appears before that of thyroid hypofunction. Signs of adrenal insufficiency may only become clinically apparent if the patient is subjected to some stress, such as a surgical operation, when fatal collapse may suddenly ensue.

The ability of the patient with hypopituitarism to maintain the blood pressure and avoid dehydration and other hazards of salt and water metabolism encountered by the patient with adrenal insufficiency due to Addison's disease is related to the continued secretion of aldosterone in near normal amounts. The secretion of aldosterone is controlled by a trophic hormone ('aldosterone stimulating hormone') which is not liberated by the pituitary and although corticotrophin (ACTH) has a minor role in controlling the amount of aldosterone released, destruction of the pituitary does not result in the loss of this important electrolyte-regulating hormone, so that renal loss of sodium can be minimized. These patients can adapt to reduction of sodium intake adequately. Loss of secretion of hydrocortisone results in an impaired ability to excrete water. Most patients with hypopituitarism adapt to this by drinking very little fluid and have a low urine volume. They may dilute down their plasma sodium concentration to very low levels, e.g. 110 mEq/l., and feel well if somewhat tired. Admission to hospital where the low urine volume may be noted and lead to forcing fluids, may end disastrously by resulting in water intoxication.

It follows from the above that it is of the utmost importance to assess endocrine function before operation on the tumour since this may well precipitate an adrenal crisis. Grant (1948) records 8 deaths in 71 cases due to this cause in the immediate post-operative period.

Clinically, one important pointer to the existence of hypopituitarism is pallor and loss of pigmentation, particularly around the areolæ and in scars. This pallor has two components; one is anæmia, but the pallor is out of proportion to the anæmia and is accounted for by the loss of melanophore-stimulating hormones secreted by the pars intermedia of the pituitary and perhaps to loss of ACTH which has some melanophore-stimulating activity. Loss of body hair is another useful sign. Particular reference should be paid to gonadal function when the history is taken since, as already stated, this may antedate signs of thyroid or adrenal insufficiency by years.

Various tests of endocrine function have been suggested. For practical purposes, failure of the adrenal and thyroid glands is important over the period of operation. Thyroid function is easy to estimate, a twenty-four-hour radioactive iodine uptake being sufficient for the purpose and available in most hospitals. In parenthesis, the plasma cholesterol is normal or low in pituitary hypothyroidism, perhaps due to loss of androgens. Adrenal function is more important and more difficult to assess. One test can be dismissed immediately as too dangerous to perform, namely, insulin sensitivity. Patients with hypopituitarism show hypoglycæmia unresponsiveness and may die in irreversible hypoglycæmia if given insulin. Another, the water load test, can also be dangerous since these patients are unable to excrete more than 10–15% of water load. The administration of a litre or so of water in the performance of this test may lead to water intoxication (Wynn & Garrod 1955). The water load test is non-specific. If abnormal, it must be demonstrated that the administration of 100 mg of cortisone is capable of reverting the test to normal. The most certain way of assessing adrenal function is to measure blood corticoids or urine 17-ketogenic steroids and assess the response to ACTH. In patients with hypopituitarism virtually no response occurs for a couple of days and then slowly climbs to normal.

Patients with primary pituitary tumours very seldom exhibit diabetes insipidus, although the posterior lobe of the pituitary may be destroyed. Recent observations on experimental diabetes insipidus in animals have shown that the classical view, that the posterior lobe of the pituitary was responsible for the elaboration of anti-diuretic hormone (vasopressin), was erroneous. It is now believed that vasopressin is secreted in the cells of the supra-optic and paraventricular nuclei of the hypothalamus and pass down the pituitary stalk to the posterior lobe of the pituitary, which serves as a storage organ (Sharrer & Sharrer 1954). It can be liberated direct from the hypothalamus, so that for permanent diabetes insipidus to ensue there must be destruction of the secretory part of this system, namely the hypothalamic nuclei. Chromophobe adenomata rarely do this. Suprasellar tumours such as craniopharyngiomata can; secondary carcinomatous deposits, or granulomata such as sarcoid, are commoner causes. It should be noted that anterior pituitary failure, leading to loss of glucocorticoids and consequent impairment of water excretion, may mask the manifestations of diabetes insipidus, which will then only become apparent when cortisone replacement therapy is given. The hormonal deficiencies of hypopituitarism can be adequately treated by the administration of cortisone,

25–37·5 mg/day, and l-thyroxine, 0·1–0·3 mg/day. Testosterone œnanthate, 250 mg every three to four weeks intramuscularly will compensate for loss of androgenic secretion. Thyroxine should not be given without cortisone since this may precipitate an adrenal crisis.

Although chromophobe tumours of the pituitary are much more common than are eosinophilic and basophilic, endocrine interest has centred on the latter types, since these tumours were believed to be sources of trophic hormones, whereas chromophobes, were thought to be inactive in this respect.

The eosinophilic cell secretes growth hormone; eosinophilic tumours are associated with acromegaly in adults or gigantism if they develop before the epiphyses have fused. The characteristic skeletal changes of acromegalics are well known, and are often accompanied by arthritic pain. These patients often have psychological difficulties, and suffer from headaches. Acromegaly is a self-limiting disease; the skeletal changes are irreversible so that it is difficult to assess activity of the tumour. Growth hormones decrease the renal excretion of phosphate, so that an elevated plasma phosphorus concentration, in the absence of uræmia, is indicative of activity. Impaired glucose tolerance may also be present. Ballooning of the sella turcica with encroachment on the optic chiasma is common; McCullagh & Brandon (1960) report that 68% of their series showed X-ray evidence of enlargement of the sella whilst 50% had visual field defects, usually upper temporal quadrant defects which may ultimately lead to blindness.

Basophil adenomata of the pituitary are classically associated with Cushing's syndrome. These adenomata are not found in all cases of Cushing's syndrome and when they do occur, their role in its pathogenesis is uncertain. Basophil adenomata are composed of β- and δ-cells; it is thought that β-cells secrete ACTH, but whether excessive amounts of ACTH are secreted in Cushing's syndrome is still a matter which awaits the development of more sensitive methods of detecting this hormone. Basophil adenomata are small and to my knowledge none has been reported which expanded the sella turcica, hence they do not give rise to visual disturbance.

Of great interest is the recent recognition of the development of chromophobe adenomata of sufficient size to enlarge the sella turcica and produce symptoms in patients bilaterally adrenalectomized for Cushing's syndrome (Nelson *et al.* 1958). Such tumours may make their presence known several years after adrenalectomy in cases where before operation there was no detectable tumour present. This is not to say that a small chromophobe adenoma was not initially present; such tumours have been recognized as a cause, or at least to be associated with, Cushing's syndrome (Marks 1959). These tumours, composed of γ-cells or amphophils, secrete ACTH in amounts much greater than those encountered in Cushing's syndrome before operation, suggesting that removal of the end-organ has stimulated their growth and activity. Chromophobe adenomata have also been noted in acromegaly. The classical view that chromophobe adenomata are composed of non-secreting cells is therefore erroneous; some of these tumours, at least, are composed of cells of great metabolic activity.

Finally there are those who believe that all chromophobe adenomata arise as the result of, not the cause of, end-organ failure. This view is based largely on the long latent interval – in some cases decades – which may elapse between the first symptom or sign referable to hypopituitarism and the clinical recognition of the presence of a chromophobe adenoma. It is said that a curious people called the Skopecs, who practise ritual castration, have an unusually high incidence of chromophobe tumours (Tandler & Gross 1910). However, if this theory were true, patients with Addison's disease and myxœdema should develop chromophobe tumours and the incidence of such tumours in these diseases is no higher than normal. The role, if any, which target gland failure plays in the pathogenesis of pituitary tumours in man is thus still far from clear, although animal work has shown that chromophobe adenomata can be produced experimentally, e.g. by thyroidectomy in mice (Furth & Clifton 1958).

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Pathology of Human and Experimental Pituitary Tumours

by C Treip MD (*London*)

A pituitary neoplasm may arise in the anterior or posterior lobes and, if it remains small, keeps an intrasellar position below the diaphragma sellæ (Fig 1). It is more common, however, for the tumour, by expansion, to become extrasellar; and some tumours may be extrasellar from the

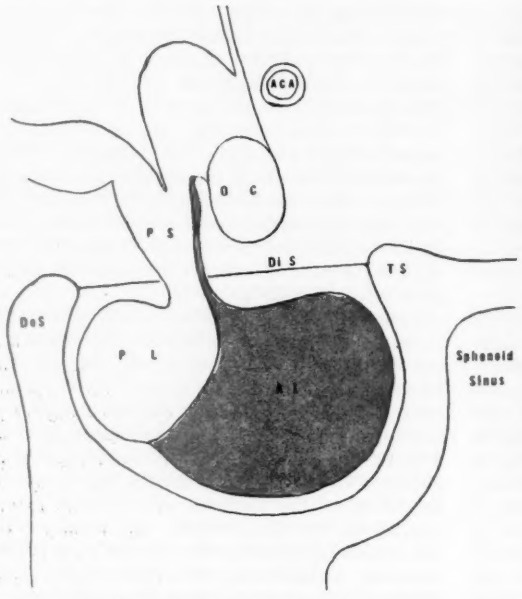

Fig 1 *Diagram of anatomical relations of the pituitary gland (sagittal section).* ACA, *anterior cerebral artery;* AL, *anterior lobe;* Di S, *diaphragma sellae;* Do S, *dorsum sellæ;* OC, *optic chiasma;* PL, *posterior lobe;* PS, *pituitary stalk;* TS, *tuberculum sellæ*

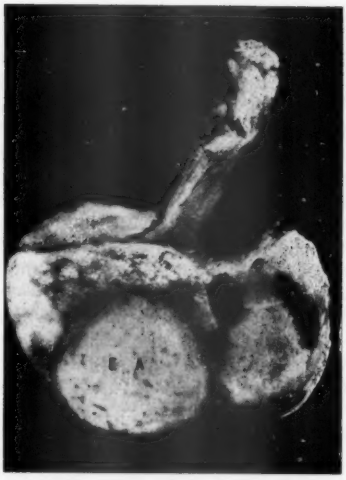

Fig 3 *Small intrasellar eosinophil adenoma (EA), which produced acromegaly.* ×4

Fig 2 *Encapsulated pituitary adenoma seen from below. The optic nerves have been stretched upwards and forwards, impinging on the anterior cerebral and communicating arteries, which are grooving the optic structures. The arrow shows the marked kinking at the optic foramen.* ×1·3 *approx.*

start if they arise from the pituitary stalk, which is continuous with the posterior lobe, or from the pars tuberalis, which is in continuity with the anterior lobe. Any tumour arising from this region, whether a pituitary tumour or a tumour of the surrounding bone, meninges or nervous tissue – the hypothalamus and optic pathways – can produce the same pressure effects, such as hypopituitarism by destruction of the functioning pituitary gland, hypothalamic disturbances, or visual symptoms.

The relation of the anterior cerebral artery to the optic chiasma is important in the pathogenesis of visual symptoms (Kernohan & Sayre 1956). Fig 2 shows a large chromophobe adenoma (seen from below) which has grown out of the sella and pushed the stretched optic chiasma and nerves against the resistant anterior cerebral arteries, which have deeply grooved the optic structures. In addition, the distortion of the optic nerves has produced a sharp bend at the level of the optic foramen. Such mechanical pressures may explain in part these patients' visual disturbances.

Tumours of the Anterior Lobe

Chromophobe adenoma, the most common pituitary tumour, is usually endocrinologically non-functional, and as the onset of hypopituitarism may be insidious, the growth may reach a large size before clinical detection. The tumour may be cystic, hæmorrhagic or undergo massive infarction, but is not usually malignant, tending rather to compress surrounding structures or to

track along the cerebral fissures. Jefferson (1955) described 14 cases of pituitary adenoma in which the growth had invaded surrounding tissues such as the cavernous sinus and the sphenoid sinus; though histologically these tumours were sometimes anaplastic, there was no proved case of metastasis and Jefferson called them 'invasive adenomas' rather than carcinomas.

Signs of endocrine over-activity, such as acromegaly, Cushing's syndrome, or thyrotoxicosis may occur with chromophobe adenoma, occasionally with concomitant hypopituitarism. Many of the so-called chromophobe cells are, in fact, weakly basophilic and have been described as 'amphophilic'; they are regarded as the probable source of thyrotrophic hormone (Russfield 1958). Some patients may have other functioning endocrine tumours, most commonly parathyroid or islet cell adenoma, as well as a pituitary adenoma (Underdahl *et al.* 1953).

Eosinophil adenoma may produce acromegaly while still small and intrasellar (Fig 3), or may reach a large size and cause visual symptoms. In Jefferson's series of invasive adenomas there was a slight preponderance of the eosinophil type. Not infrequently a biopsy report will record the finding of a mixed eosinophil and chromophobe picture and sometimes a purely chromophobe structure is found. The acromegalic symptoms may be slight and overshadowed by the development of hypopituitarism – the 'fugitive acromegaly' of Cushing (1932).

Basophil adenoma: Basophil hyperplasias or adenomas are usually microscopic and the original thesis of Cushing (1932) that these tumours formed the pathological basis of Cushing's syndrome is no longer accepted. Kernohan & Sayre (1956) now state that no proved case of basophil adenoma causing Cushing's syndrome was found in their series of 600 pituitary tumours. A malignant basophil adenoma with hepatic metastasis has, however, been recorded by Cohen & Dible (1936). Fifteen of the 18 cases of Cushing's syndrome with pituitary tumours reviewed by Marks (1959) had chromophobe adenomata. Whether these chromophobe tumours are functionally responsible for the syndrome is questionable, as the patients may respond favourably to adrenalectomy. It has also been noted, however, that such tumours may manifest themselves *after* adrenalectomy for Cushing's syndrome (Montgomery *et al.* 1959) suggesting a parallel with experimental pituitary tumours. The primary site of the disturbance of endocrine homeostasis in Cushing's syndrome may, therefore, not be hypophysial but adrenal, or possibly hypothalamic.

In general, the morphological classification of pituitary adenomata has become less rigid with the further development of the concept of endocrine interdependence and of hypothalamic control.

Craniopharyngiomata have been postulated as arising from nests of squamous epithelium in the pars tuberalis; as most of the pars tuberalis is above the diaphragma, the tumours are usually suprasellar. There is a discrepancy in this theory, as cell nests are not commonly found in the pituitary before the third decade of life, whereas craniopharyngioma is commonly a tumour of the first two decades. Kernohan & Sayre (1956) suggest that metaplasia may occur in the pars tuberalis from chromophobe cells to squamous epithelium and that the tumours arise from such metaplastic foci. The tumour may be as large as a chromophobe adenoma and is usually cystic in part, containing gelatinous or oily material, with cholesterol crystals. The solid portions of the tumour are often calcified. They are not usually malignant. The presence or absence of keratohyaline granules in the squamous epithelium lining the cysts is used by Kernohan & Sayre (1956) to distinguish these tumours from epidermoid or teratomatous cysts which rarely arise in a parapituitary position.

Fig 4 *Optic glioma (astrocytoma). The hypothalamic area is occupied by a solid tumour, over which the oculomotor nerves are stretched. The optic nerves* (ON) *and chiasma are infiltrated and expanded by the tumour.* × *1·3 approx.*

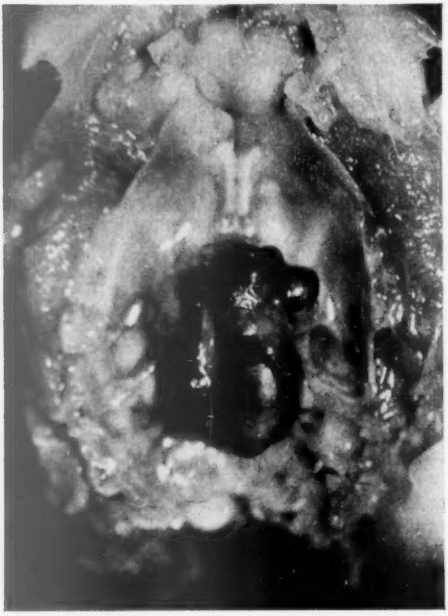

Fig 5 *Œstrogen-induced pituitary tumour occupying nearly one-third of a rat's cranial cavity. The optic nerves are seen above the tumour.* ×3·3

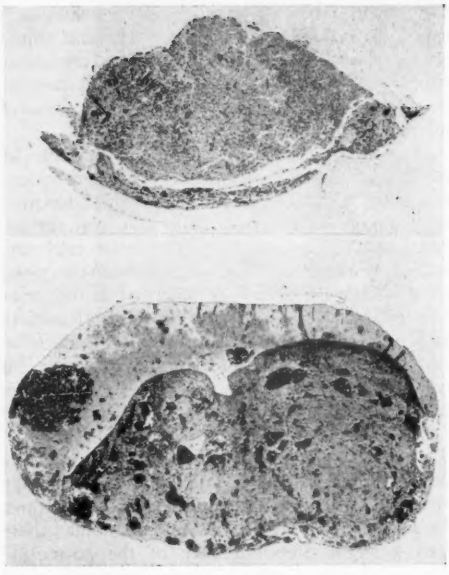

Fig 6 *Above: œstrogen-induced intermediate lobe hyperplasia in the golden hamster. The tumour has invaded and partly replaced the posterior lobe. The anterior lobe is seen as a thin band inferiorly.* ×18. *Below: œstrogen-induced tumour of anterior lobe in albino rat. The tumour is separated from the faintly marked and stretched posterior lobe (seen superiorly) by the cystic intermediate cleft.* ×13

Tumours of the Posterior Lobe

It is difficult to be sure that a gliomatous tumour in the pituitary region is a true neoplasm of the neural lobe, as extrasellar expansion will render distinction from a glioma of the diencephalon or optic pathways virtually impossible. Scothorne (1955) was, however, able to demonstrate a small astrocytoma which was confined to the posterior lobe and did not extend above the diaphragma sellæ. The 3 tumours described by Wolman (1959) as 'infundibuloma' did not involve the pituitary gland and were presumed on histological grounds to have arisen from the infundibular region. Astrocytoma of the optic pathways can have a similar structure of pilocytic astrocytoma, and can sometimes be differentiated by its selective involvement of the optic nerves (Fig 4).

Small nodules of granular cells are not uncommonly found in the neurohypophysis and tumours composed of such cells have occasionally been described (Harland 1953). Liss & Kahn (1958) suggest that such a tumour should, on morphological grounds, be called 'pituicytoma'. Rarely, a tumour resembling a pineal tumour may arise in the infundibulum – the 'atypical teratoma' or 'ectopic pinealoma' of Dorothy Russell (1954).

Secondary Tumours

These may arise as a result of direct extension from the skull or by metastasis. The most common tumour is secondary carcinoma of the posterior lobe and examination of biopsy material from therapeutic hypophysectomies reveals a number of small, symptomless metastases to this lobe. In my own limited experience of post-mortem cases of secondary growth in the anterior lobe, such growths have been accompanied by invasion of the surrounding bone, suggesting contiguous spread.

Experimental Pituitary Tumours

There is a well-known tendency in the ageing rat to the spontaneous appearance of pituitary chromophobe adenomata. It is possible, however, by experimental interference with endocrine homeostasis, to produce pituitary adenomata in rats and mice with constancy and at a comparatively early age. The simplest method is the administration of œstrogens, either diethylstil-

bœstrol or œstradiol benzoate. Earlier workers gave œstrogens by subcutaneous injection over long periods of time, but the subcutaneous implantation of a single 10 mg pellet will work as well. Other methods for producing these tumours are various forms of thyroid ablation or suppression, ionizing irradiation of the whole body, and castration.

The tumours resulting from different methods show important differences in their behaviour (Furth & Clifton 1958). Whereas those resulting from administration of œstrogens are often endocrinologically non-functioning chromophobe hyperplasias which produce the signs of hypopituitarism, those resulting from antithyroid procedures, though histologically chromophobe, have a thyrotrophic effect; the tumours resulting from ionizing irradiation may be adrenotrophic, causing eosinopenia and lymphopenia, or mammotrophic, producing hyperplasia of the mammary glands. The mammotrophic tumours are often eosinophil. Castration or ovariectomy can produce basophil adenomata (Griesbach & Purves 1960).

Œstrogen-induced adenomata may be large enough to cause proptosis and raised intracranial pressure, which can be confirmed *post mortem* by the demonstration of cerebellar herniation through the foramen magnum. The tumour can weigh fifty times the normal weight of the gland and constitutes, as might be expected from the clinical manifestations, a massive space-occupying lesion (Fig 5). Accompanying the tumour are signs of hypopituitarism, such as complete cessation of growth, advanced testicular atrophy, moderate suprarenal atrophy, and mild thyroid hypofunction, as judged histologically by slight flattening of thyroid acinar epithelium.

A species difference in the response of the pituitary to œstrogen implantation is seen in the golden hamster. Whereas the tumours of rats and mice are derived from the anterior lobe cells, in the hamster it is the pars intermedia that responds to the growth stimulus (Fig 6), invading and partly replacing the posterior lobe (Vazquez-Lopez 1944). Reflecting this difference in morphology is the hypothalamic response to the tumour; the rat's hypothalamus, though severely compressed by the tumour, shows no atrophy of the supraoptic and paraventricular nuclei, and abundant neurosecretory substance is present in these nuclei. The corresponding nuclei of the hamster, on the other hand, show a loss of neurosecretory activity and perhaps a loss of nerve cells, consequent, presumably, on the destruction of the neural lobe by the tumour. This difference in response to a given stimulus may indicate a species difference in hypothalamohypophysial mechanisms.

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Liss L & Kahn E A (1958) *J. Neurosurg.* **15, 481**
Marks V (1959) *Acta endocr., Copenhagen* **32, 527**
Montgomery D A D, Welbourn R B, McCaughey W T E & Gleadhill C A (1959) *Lancet* ii, 707
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Scothorne C M (1955) *J. Path. Bact.* **69, 109**
Underdahl L O, Woolmer L B & Black B M (1953) *J. clin. Endocrin.* **13, 20**
Vazquez-Lopez E (1944) *J. Path. Bact.* **46, 1**
Wolman L (1959) *J. Path. Bact.* **77, 283**

Meeting October 13 1960

The following cases were shown

Aberrant Retinal Tissue at the Optic Disc
Dr A N Ashworth and Dr C Pedler
Conjunctiva Lymphoma
Dr S J Crews and Dr R Barry
Some Aspects of Ocular *Toxocara canis* Infestation
Dr I Duguid
Ocular Molluscum Contagiosum
Dr P Watson and Mr Barrie R Jones
Pseudomelanoma of the Conjunctiva
Mr N Cridland and Professor N Ashton

Meeting December 8 1960

A **Forum** was arranged in which the following took part: Mr A G Cross, Mr L P Jameson Evans, Mr John Foster and Mr L H Savin.

Meeting March 9 1961

The following papers were read:

Optical Basis of Corneal Transparency
Dr D Maurice (*London*) (*see* Maurice D M, 1960, in: Symposium on the transparency of the cornea. Edited by Sir Stewart Duke-Elder and E S Perkins. Oxford; p 41)
Physiological Aspects of Corneal Transparency
Dr H Davson (*London*)

UNIVERSITY OF MICHIGAN LIBRARIES

Books recently presented and placed in the Society's library

(*Continued from page 594*)

Storch C B
Fundamentals of clinical fluoroscopy, with essentials of roentgen interpretation
pp 196 50s
London: Heinemann 1951

Strong R P *ed*
The African Republic of Liberia and the Belgian Congo. Based on the observations of the Harvard African Expedition, 1926–27
2 vols
Cambridge, Mass.: Harvard University Press 1930

Taussig H B
Congenital malformations of the heart
pp 618
New York: Commonwealth Fund 1947

Uffreduzzi O
Trattato di patologia chirurgica generale e speciale
2 vols
Torino: Unione Tipgrafico—Editrice Torinese 1933–1934

Vilaseca Sabater J M & Barcelo P
Patología de la pequeñas articulaciones intervertebrales: clínica y radiología
pp 131
Barcelona: Salvat Editores 1946

Wagner E G & Lanoix J N
Water supply for rural areas and small communities
pp 337 35s
Geneva: World Health Organization 1960

Wagner E G & Lanoix J N
Excreta disposal for rural areas and small communities
pp 187 25s
Geneva: World Health Organization 1958

Wakeley C P G & Orley A
A textbook of neuro-radiology
pp 336
London: Baillière 1938

Weber F P
Miscellaneous notes
8th series pp 12
London: Lewis 1960

Wheeler A & Jack W R
Wheeler's handbook of medicine by William R Jack
5th ed pp 552
Edinburgh: Livingstone 1916

Williams C M jr
Thyroid scanning
pp 100
Washington: U S Government Printing Office 1960

Williams R E O *et al*
Hospital infection: causes and prevention
pp 307 35s
London: Lloyd-Luke 1960

Wolf S G & Wolff H G
Human gastric function: an experimental study of a man and his stomach
2nd ed pp 262
London &c: Oxford University Press 1947

World Health Organization. Regional Office for Europe
European Seminar for Sanitary Engineers
Design and operation of septic tanks
3rd European seminar. 27 October–1 November 1952, WHO, Monograph Series No 18
pp 122 7s 6d
Geneva: World Health Organization 1953

World Health Organization
Advances in the control of zoonoses. WHO/FAO Seminar on Zoonoses
pp 275
Geneva: World Health Organization 1953

World Health Organization
International standards for drinking-water
pp 152 20s
Geneva: World Health Organization 1958

World Health Organization
World directory of venereal-disease treatment centres at ports. Application of the International Agreement of Brussels, 1924
pp 162 8s 6d
Geneva: World Health Organization 1959

World Health Organization
Bibliography on bilharziasis 1949–1958
pp 158 10s
Geneva: World Health Organization 1960

Wranne L
Free erythrocyte copro- and protoporphyrin: a methodological and clinical study
pp 78
Uppsala: Almqvist and Wiksells 1960

Wynn-Parry C B
Rehabilitation of the hand
pp 273
London: Butterworth 1958

Younger E G
Insanity in every-day practice
3rd ed pp 130
London: Baillière 1914

Ziemann H
Hämatologisches Praktikum für Studierende und Ärzte
pp 166
Berlin: Karger 1927

Section of Pathology

President N F Maclagan MD

Meeting January 17 1961

Papers

Bacterial Population Studies in Chronic Murine Tuberculosis [*Abridged*]

by R J W Rees MB BSC (*London*)

Tuberculosis, both in man and experimental animals, can manifest itself in almost any degree of severity and progression, from a relatively acute and progressive generalized infection to one in which the infection remains localized and apparently stable. The latter type of disease is a manifestation of partial immunity, in which not all tubercle bacilli are destroyed and in which the surviving bacilli remain in equilibrium with the host, often for long periods. Analysis of the resulting host-parasite equilibrium is pertinent to our understanding of the type of immune process frequently seen in tuberculosis, the state of bacilli in a stable infection, the viability of bacilli in such an infection and the choice of treatment for the chronic type of infection, which even in this successful era of chemotherapy is the more difficult type of infection to treat.

In mice, chronic tuberculosis can readily be produced as a predominantly pulmonary infection either by giving small doses of tubercle bacilli (Hart & Rees 1950, 1960), or by challenging with larger doses of bacilli following vaccination with BCG (Sever & Youmans 1957). The resulting infections are a manifestation of partial immunity, either to the primary infection or to the vaccination. Under both conditions of infection the majority of the mice remain alive for many weeks, appear healthy and gain weight, yet they have obvious pulmonary lesions in which there are many acid-fast bacilli which grow readily on culture. It appears a stable pulmonary disease with a steady viable bacillary population in the lungs, although under certain stresses this infection can break down and the bacilli freely multiply. For example, when such mice are given cortisone, the infection spreads and these animals may die within twenty days with a great increase in the number of bacilli in the lungs (Hart & Rees 1950). Where the number of viable tubercle bacilli have been counted in the lungs of the mice during the chronic infection, the results suggest that the bacilli remain alive but do not divide – 'a static equilibrium' – yet evidence based on viable counts alone does not exclude a 'dynamic equilibrium'. This equilibrium was therefore analysed further by following in parallel the viable and the total (stainable) bacillary populations in lung homogenates from mice with untreated chronic tuberculosis (Hart & Rees 1960). The total counts from the lungs remained steady and were similar to the viable counts from day 60 to day 138. The results indicated that unless dead organisms were being removed from the lungs or that their acid-fastness was being lost, the bacillary population was viable and not multiplying.

In order to see what happened to dead bacilli in the lungs of such mice, a group of animals was given a powerful bactericidal combination of drugs. By disturbing the host-parasite equilibrium in this way it was hoped to follow the fate of the killed bacilli in the lungs. A combination of isoniazid and pyrazinamide was chosen since, from the work of McCune *et al.* (1956), this appears to be the most powerful bactericidal combination for mice. A composite picture of the results obtained (Rees & Hart 1961) are shown in Fig 1. Although the viable counts fell steeply throughout the treatment period, total counts remained high and fell only slowly, after three weeks' treatment, below the total counts of the untreated mice. These results indicated that a high proportion of the dead bacilli (killed by treatment with isoniazid and pyrazinamide) were not removed from the lungs and retained their acid-fastness. It is concluded, therefore, that in chronic murine tuberculosis, the bacilli are in a static or resting phase, rather than in a 'dynamic equilibrium' between multiplication and destruction.

It is likely that in man there may be similar situations either in the lungs or in other organs

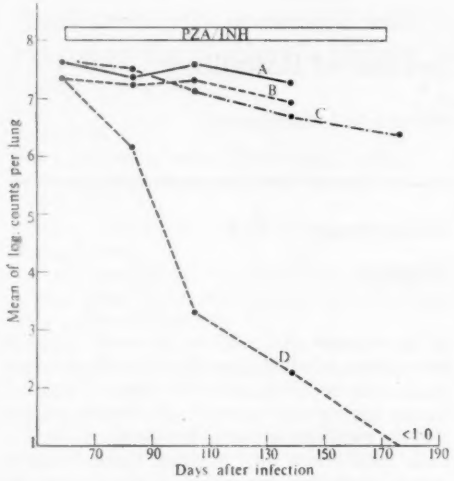

Fig 1 *Viable and total population of* Myco. tuberculosis *in mouse lungs during a chronic infection (0·02 mg H37 Rv) and effect of combined treatment with pyrazinamide-isoniazid, PZA/INH (data from Rees & Hart 1961).* A= *untreated, total count.* B= *untreated, viable count.* C= *PZA/INH, total count.* D= *PZA/INH, viable count.* (*By courtesy of the Editors of the* British Journal of Experimental Pathology)

where viable bacilli, though in a resting phase, may remain for long periods. It is of interest to know which drugs or combination of drugs have activity against such a resting population. From our own results it is obvious that a powerful combination of bactericidal drugs, such as isoniazid and pyrazinamide, can kill bacilli even when they are in a non-dividing state. It is equally clear from the work of McCune & Tompsett (1956) with *p*-aminosalicylic acid and of Hart & Rees (1960) with macrocyclon, that these bacteriostatic drugs have little or no effect against chronic infection in mice. Yet both these drugs, in particular macrocyclon, have considerable activity against an acute infection in mice – where the bacterial population is a freely multiplying one. The contrast between the effectiveness of macrocyclon and *p*-aminosalicylic acid *in vivo* against an acute infection, and their ineffectiveness against a chronic infection, is almost certainly a reflection of similar contrasts between the action *in vitro* of other bacteriostatic drugs on multiplying and non-multiplying bacilli (Singh & Mitchison 1955, Hobby & Lenert 1957). McCune *et al.* (1956) also found little or no evidence of drug resistance during the treatment of chronic murine infections. This is probably because resistant variants could not grow out from a predominantly resting population of bacilli.

The dual counting technique, including the counting of total numbers of stained bacilli in the lungs, shows that even when a very high proportion of the bacilli are killed by chemotherapy they can remain in a stainable form *in situ* for many weeks. From other experimental work this finding is not unexpected since it is known that dead pathogenic mycobacteria injected into animals remain *in situ* in a stainable state for very long periods. In man, in contrast with mice, the pulmonary lesions remain open and killed bacilli are readily shed into the bronchi. Also in man, stainable but culture-negative bacilli are not uncommonly found, particularly after chemotherapy, in the closed 'round lesions' in the lungs and other isolated sites in the body. It has been suggested that these organisms are not really dead but only modified by chemotherapy and unable to grow in the usual culture media. Our experimental findings are against this hypothesis because they clearly show that acid-fastness can persist *in vivo* long after the organism is dead.

This work has been carried out in collaboration with my colleague Dr P D'Arcy Hart.

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Anonymous Mycobacteria as a Cause of Phthisis

by J Marks MD MRCP (*Cardiff*)

The diagnosis of phthisis by bacteriological methods dates from 1882 but it was not until some decades later that the cultivation of tubercle bacilli became widely practised. From that time, reports began to appear in the literature of unusual mycobacteria isolated from apparently typical cases of tuberculosis. Although most of the early observations were limited to one or two cases, several authors recognized and discussed fully the significance of these mycobacteria (e.g. Beaven & Bayne-Jones 1931); but little general interest was aroused in either the organisms or the disease with which they were associated. That situation has now changed. The reports have multiplied and the subject has become familiar to all interested in chest disease. Two factors especially have been responsible for this development. First, the introduction of chemotherapy for tuberculosis not only led to a demand for many more cultures for the purpose of sensitivity tests,

but also obliged the bacteriologist to consider carefully the characteristics of individual strains. Consequently, some organisms which formerly would have been accepted as tubercle bacilli are now recognized as being distinct. Secondly, the recession of tuberculosis in many countries has thrown these anomalous infections into greater prominence. It is possible also that, in addition to better recognition, there has been a true increase in incidence in recent years.

The mycobacteria under consideration have no accepted name. It is convenient therefore to use the provisional name 'anonymous mycobacteria' suggested by Runyon (1959). The disease caused by anonymous mycobacteria also has no name and for this I have suggested elsewhere the term 'mycobacterial' pseudotuberculosis' (Marks & Trollope 1960).

Ætiology

The incidence of mycobacterial pseudotuberculosis appears to vary considerably in different parts of the world but interest in the disease and facilities for its recognition are so unevenly distributed that it will be some time before an accurate picture can be obtained. It is already clear, however, that different varieties of anonymous mycobacteria predominate in different areas. All reports agree that men are much more commonly affected than women and that most infections occur in middle age or later. Not infrequently the disease is found in association with pneumoconiosis or aspiration pneumonia and it seems likely that these lung affections are local predisposing factors. In some instances there appears to be a general predisposition to mycobacterial infection as a consequence of malnutrition or, as in two of my own cases, steroid therapy. Although an accurate estimate is not yet possible, I would place the incidence of mycobacterial pseudotuberculosis in Great Britain at about 200 new cases a year.

Pseudotuberculosis does not appear to be infectious to contacts. Infection must therefore arise from human carriers, from animals or from free-living organisms. A survey in a rural area of Georgia demonstrated mycobacteria in the saliva or sputum of 16 out of 122 healthy people (Edwards & Palmer 1959). However, these mycobacteria may have been free-living organisms recently inhaled or ingested in an area where they are prevalent. In contrast, Dr Erin and I failed to isolate anonymous mycobacteria from samples of sputum or saliva submitted by about 4,000 members of the general public in an area of South Wales. Little is known of infection, carriage or excretion by animals. It is of interest, however, that cows may become sensitized to mycobacterial antigens in circumstances that make tuberculosis unlikely; also that a number of anonymous strains cannot be distinguished from avian-type tubercle bacilli which have lost virulence. Nevertheless, the origin of most anonymous mycobacteria is probably the great reservoir of free-living mycobacteria. These are known to include species with a certain degree of pathogenicity such as *Mycobacterium balnei*.

Classification

On the whole, pulmonary and non-pulmonary forms of pseudotuberculosis are distinct. Extension of lung infection to give empyema or metastatic lesions does occur but is uncommon. Non-pulmonary disease mostly takes the form of cervical adenitis or skin lesions. In the case of cervical adenitis at least, a special type of organism is frequently responsible which is rarely found in lung infections.

Morbid Anatomy and Bacteriology

The macroscopic and histological appearances of lung lesions cannot be distinguished with certainty from those of tuberculosis. In abscesses, as noted by Cobbett (1918), the leucocytes maintain their structure much better in pseudotuberculosis than in tuberculosis.

Bacteriological diagnosis is made by the use of a number of cultural and biochemical tests (Marks & Trollope 1960); animal inoculation is only required to ensure that virulent tubercle bacilli are not being masked. Repeated isolations are essential for diagnosis as the anonymous mycobacteria cannot always be distinguished from the saprophytic or commensal organisms which occasionally get into specimens by accident.

Runyon (1959) showed that the anonymous mycobacteria can be divided into three main groups on the basis of pigmentation. These are as follows:

I Photochromogens, which are cream or buff when growing in the dark but which develop a yellow or orange colour rapidly when grown after exposure to light.

II Scotochromogens, which are yellow, orange or reddish from the onset of growth whether in the light or dark.

III Nonphotochromogens, which are cream or buff both in the light and dark although a number of strains produce other pigment on prolonged incubation.

Most Group I strains are isolated in circumstances suggesting pathogenic activity. In contrast, Group II strains are usually casual intruders except for a sub-group with distinct properties, which are especially associated with cervical adenitis. Group III is also mixed. The members which grow slowly often prove to be pathogens and those that grow fast are usually strains with-

out significance. Nevertheless, fast growers cannot be dismissed without investigation as they are undoubtedly responsible for some cases of pseudotuberculosis.

Symptoms and Signs
Pseudotuberculosis produces symptoms and signs similar to those of the less acute forms of tuberculosis. As with tuberculosis, symptomless lesions occur which are disclosed by radiography and are identified by bacteriological examination. The infection is sometimes overlooked when superimposed on chronic lung disease, deterioration of the patient's condition being then attributed to the underlying disease. Hæmoptysis and cavitation are somewhat more frequent in pseudotuberculosis than in tuberculosis and the lesions are more often unilateral and localized. However, the radiological appearances are not certainly distinguishable in the two infections.

Diagnosis
The distinction from tuberculosis is made on bacteriological grounds. The organism has to be distinguished from a tubercle bacillus and must be isolated repeatedly from the lesion or morbid materials (usually sputum). Before a diagnosis of pseudotuberculosis is made it is advisable to exclude the possibility that tubercle bacilli are being masked by inoculating one guinea-pig with a primary culture and another directly with morbid material, suitably decontaminated. If additional evidence is required, comparative skin tests may be made with tuberculin and protein prepared from the suspected pathogen.

Treatment and Prognosis
The severity of pseudotuberculosis varies considerably. Some patients recover spontaneously, but on the whole the prognosis is worse than in tuberculosis. The difficulty is that anonymous mycobacteria as a group are not very susceptible to the drugs developed for the chemotherapy of tuberculosis. It is not possible at present to offer much general guidance on chemotherapy. All the strains we have tested at Cardiff have been resistant *in vitro* to P.A.S. and pyrazinamide, but susceptibility to other drugs varied in different cases. The nonphotochromogens are the least susceptible group. It is not yet clear how reliable *in vitro* tests are as a guide to chemotherapy.

Excision of the lesion gives good results when it is practicable. The outlook is much less favourable with medical treatment. A study recently made by the Pneumoconiosis Research Unit has shown that this is particularly the case when the infection complicates pneumoconiosis (Kamat *et al.* 1961).

As the risk to contacts appears to be negligible, there is no need to isolate patients with pseudotuberculosis. They should not however be nursed in contact with infectious tuberculosis since instances of superinfection with tubercle bacilli have been reported (Lewis *et al.* 1960), and their resistance to mycobacteria is almost certainly low.

General Remarks
Relatively little is known about resistance to infection by anonymous mycobacteria but it probably operates in the same way as resistance to infection by tubercle bacilli. If this is true, one might expect innate immunity to be distributed similarly in the two cases and predict that as tuberculosis is eradicated, pseudotuberculosis will become more common, for some of the people who would otherwise have fallen victim to the former will do so to the latter. Studies in progress do indeed suggest that an increase is now occurring in Britain. Fortunately, the low virulence of the anonymous mycobacteria will not allow the incidence of pseudotuberculosis to reach a level anywhere near that of tuberculosis in the recent past.

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Cobbett L (1918) *Brit. med. J.* ii, 158
Edwards L B & Palmer C E (1959) *Amer. Rev. Tuberc.* **80**, 747
Kamat S R, Rossiter C E & Gilson J C (1961) *Thorax* (in press)
Lewis A C, Lasche E M, Armstrong A L & Dunbar F P (1960) *Ann. intern. Med.* **53**, 273
Marks J & Trollope D R (1960) *Tubercle, Lond.* **41**, 133
Runyon E H (1959) *Med. Clin. N. Amer.* **43**, 273

The following paper was also read:

Attenuated Tubercle Bacilli
by Dr D A Mitchison (*London*)
A full account will be published in the *Bulletin of the World Health Organization*, in collaboration with A L Bhatia, A Csillag, W Fox, S Radhakrishna, C V Ramakrishnan, J B Selkon, P R Somasundaram, T V Subbaiah, S Velu & J G Wallace

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Meeting November 1 1960
at the Wellcome Laboratories of
Tropical Medicine Euston Road London

The following demonstrations were given:

Cestodes
O D Standen and K A Fuller

Nematodes
J E D Keeling

Trematodes
G Dickerson

Leptospira: Dark-field and Section
L H Turner

Pneumocystis carinii
C A Hoare

Retinotoxicity
L G Goodwin

Chemotherapy of Smallpox and Related Infections
D J Bauer, P W Sadler and F W Sheffield

Drawings of Phlebotomus
B Jobling

Metabolic Studies in Ascaris
M Kaighen

Microprocedures Used in Studying Helminths; Use of Chromogenic Substrates. Elements of Paper Chromatography
R H Nimmo-Smith

Experimental Infections of *Leishmania tropica* in Mice
R A Neal

Tissue Phase of *Trypanosoma cruzi* in Culture and Mouse
E Beveridge and P Rathmell

Evidence for Prolongation of Action of Primaquine Against Avian Malaria by Simultaneous Administration of Chloroquine
P Bradley

Paper Chromatography; a Colorimetric Method
C R Jones

Snail Breeding; Schistosomes and Liver Flukes
W Occomore

Meeting November 15 1960

A Discussion was held on **Leukæmia**; the opening papers were as follows:

The Nucleoprotein Content of Normal and Leukæmic Leucocytes
Dr A J Hale

The Immunology of Leukæmic Cells
Dr P A Gorer

The Choice and Control of Therapy in the Leukæmias
Dr F G H Hayhoe

Meeting February 7 1961
at University College Hospital Medical School London

The following demonstrations were given:

A Labour-saving Method for Screening Admissions for Nasal Carriage of Antibiotic-resistant Staphylococci
E Joan Stokes

Starch Gel Electrophoresis in the Diagnosis of Macroglobulinæmia
E A Butler, E M Clarkeson, F V Flynn, H Harris and E B Robson

(1) **The Differentiation of Ischæmic and Chronic Pyelonephritic Scars**
(2) **Lead Nephropathy in the Rat**
J F Smith

Unusual Gynæcological Specimens
P E Hughesdon

Recent Advances in Studies on Experimental Inflammation
W G Spector and D A Willoughby

Intracellular Potassium in Dietary Liver Necrosis
A E M McLean

The Effect of a Thyroid Hormone Analogue (TRIAC) on Rat Teeth
S Brownstone, P Hollaway, W R Merrington and R Pitt-Rivers

Experimental Stricture of the Common Bile Duct
C T Hou

Analysis of Normal Serum Components Neutralizing Influenza Virus Hæmagglutination and Infectivity:
(*a*) Chromatographic and Electrophoretic Analysis of Serum Components
(*b*) Chemical Estimation of Sialic Acid
(*c*) Study of Virus Neutralization
(*d*) Periodic Variation in the Inhibitor Spectrum of Influenza Virus Strains
G Belyavin, A Cohen and F Biddle

Study of Poliomyelitis Antibodies by Diffusion Methods
P G Higgins

Metabolic Studies on the Isolated Liver Cell Nucleus from Normal and Pre-cancerous Livers
H Rosa and G Rowland

The Pathogenesis of Experimental Liver Injury and the Possibility of Protection
K R Rees and V Shotlander

Metabolic Regulation in the Hepatic Cell. The Simultaneous Determination of Diphosphopyridine and Triphosphopyridine Nucleotides (DPN/DPNH and TPN/TPNH), to Provide a Measure of Biochemical Disturbance in Liver Disease
T F Slater

Nervous and Biochemical Disturbances Following Hexachlorobenzene Intoxication
F De Matteis, B E Prior and C Rimington (*see Nature, Lond.* in press)

***In vitro* Studies of Hæmopoiesis in Spleen and Bone Marrow of Normal and Polycythæmic Mice**
J Wildy and P M Cotes

Biochemical Changes in Aphakia and their Possible Relationship to the Ætiology of Retinal Detachment
H Heath, T Beck and A C Rutter

The Chemical Analysis of Subretinal Fuid and its Bearing on the Type of Detachment and the Origin of this Fluid
H Heath and T Beck

(1) **A Method of Estimating Tissue RNA and DNA using Fluorescence Microscopy** (*see* Proceedings of First Congress of Histochemistry and Cytochemistry, Paris 1960: in press)
(2) **The Physical State of the Dermis in Unfixed Skin** (*see* Jarrett A, 1958, *Brit. J. Derm.* **70**, 343)
A Jarrett

Meeting March 7 1961
at the Lister Institute of Preventive Medicine

The following specimens were shown:

Assay and Partial Purification of Human Anti-hæmophilic Factor
P W Walton and R A Kekwick

Diffusion as an Aid in the Characterization of Proteins
J M Creeth

The Detection of Platelet and Leucocyte Antibodies
K L G Goldsmith

The Application of Immunoelectrophoresis to the Standardization of Anti-human-globulin Serum
E W Ikin and K L G Goldsmith

Maps Illustrating Recent Work on Blood-group Serology
A E Mourant

Some Uses of Ficin in Blood-group Serology
C M Giles

Controlled Fragmentation of Blood-group Specific Mucopolysaccharides
W T J Morgan and T J Painter

Structure of Cardiolipin and of a Similar Phospholipid from *Micrococcus lysodeikticus*
M G Macfarlane

Studies on Starch Metabolism
B J Bines

Group Specific Polysaccharide of *Streptococcus pyogenes* having a Direct Toxic Effect on Connective Tissue of the Rabbit
J H Schwab

Blood Group Genetics: Some Recent Problems Investigated in the Unit
R R Race and Ruth Sanger

Immunology and *in vitro* Culture of African Trypanosomes
B G F Weitz, F M Lee-Jones, S M Lanham, A R Grey and M D Pittam

Pleuropneumonia-like Organisms
E Klieneberger-Nobel and R Lemcke

The Ouchterlony Technique in the Sorting of Hæmophilus Strains from Trachoma Patients
A F B Standfast and G W Sampson

Genetic and Chemical Studies of Variants of the H Antigen of *Salmonella typhimurium*
T M Joys and M W McDonough

Conjugation and Gene Transfer in Salmonella
S Smith and G G Meynell

Various Laboratory Studies of Trachoma and of Inclusion Blennorrhœa Virus
Medical Research Council Trachoma Research Unit

Book reviews

Intra-abdominal Crises
by Kenneth D Keele MD FRCP
and Norman M Matheson FRCS MRCP FACS
pp xii+397 illustrated 50s
London: Butterworths 1961

Abdominal emergencies in the past have tended to remain in the realm of the surgeon, yet every clinician knows how often these cases are the manifestations of acute medical problems, not necessarily even involving abdominal viscera. Moreover the straightforward 'surgical abdomen', in these days of an ageing population, is frequently complicated by some co-existing medical disease.

'Intra-abdominal Crises' represents an adult approach to this subject prepared by the collaboration of a physician and a surgeon. The result is a most stimulating account of the diagnosis and management of patients presenting with acute abdominal pain and vomiting. It is unusual in that it is a book which should prove of genuine value both to the hospital clinician and the general practitioner. One small criticism is the standard of reproduction of some of the radiographs – always a difficult problem for the publishers – which might with advantage be improved in later editions.

The Closed Treatment of Common Fractures
by John Charnley BSC MB FRCS
3rd ed pp xii+272 illustrated 50s
Edinburgh & London: E & S Livingstone Ltd 1961

This book is a monograph on certain common fractures. It is not a complete study of all the fractures in the body. The author confines his attention to the humerus, the radius and the ulna, Bennett's fracture, and certain fractures of the fingers, of the femur and of the tibia and fibula.

Knowledge of the repair of fractures is at present very imperfect. The author sets out to remedy this defect by drawing on the information he has obtained in his studies of compression arthrodeses of the knee. He holds that there are fundamental differences between the union of cancellous and of cortical bone. He concludes that there must be close apposition for cancellous bone to unite, whereas fractures through the shaft of the long bones unite mainly by subperiosteal new bone formation, first known as woven bone and later as lamellar bone as originally described by Professor Baker. Bony union, wherever it occurs, should be generally regarded as fundamentally similar, differing only in degree according to its site. The author very rightly points out the dangers of periosteal stripping associated with open reduction of fractures, and the evil effects of circumferential wiring of bone, which destroys the ensheathing periosteal callus. All this argues the importance of adequate blood supply for the production of new bone and the healing of fractures. The argument that operative treatment is potentially harmful to all fractures, but conservative treatment even when it fails is less harmful and is more capable of being salvaged, are facts with which very few will disagree.

Hæmophilic Diseases in Denmark
A Classification of the Clotting Defects in 78 Hæmophilic Families
by Knud-Erik Sjølin MD
pp 349 illustrated 35s
Oxford: Blackwell Scientific Publications 1961

In 1943 Andreassen surveyed the known hæmophilic patients in Denmark and his monograph has continued to be used as an authoritative description of the disease in a relatively small population. In 1943 the complications of modern coagulation theory had not subdivided the disease into four separate entities – (1) hæmophilia or factor VIII deficiency, (2) Christmas disease or factor IX deficiency, (3) plasma thromboplastin antecedent or P.T.A. deficiency, (4) Hageman defect. A reassessment of coagulation defects in this population is therefore an event in the coagulation literature.

This review includes full clinical histories and pedigrees of 148 patients from 78 families and these will be of interest to all coagulation workers. The coagulation defects in the different patients were studied, using mainly the thrombin generation test which was selected because it is 'easier to control'. The choice of this test was unfortunate because in practice it clearly did not prove easier to control than other more specific tests. In a modern coagulation laboratory most patients with coagulation defects associated with symptoms of abnormal hæmorrhage can be assigned with fair certainty to the three main categories of hæmophilic, Christmas disease and contact defects (P.T.A. deficiency, Hageman defect); this distinction is made using quantitative tests for factors VIII and IX and tests of surface contact activity. The clear distinction between Hageman defect and P.T.A. deficiency remains uncertain. In most areas hæmophilia and Christmas disease are by far the most common defects. Sjølin, using the thrombin generation test, found 31 patients in the category of contact abnormalities and the improbability of this result led him to reinvestigate

these patients when it was found that 11 had a mild degree of hæmophilia, 6 Christmas disease and 2 combined defects of Christmas factor and antihæmophilic globulin deficiency. The reader is left with a doubt whether even with this reassessment the final diagnosis reached would agree with those of other workers. This doubt is accentuated by the fact that all of the 11 patients classified as having Hageman defect suffered some abnormal bleeding. In the classical description of this defect the patients were asymptomatic.

It is, of course, possible that a different approach to the study of coagulation defects might reveal new information about ætiology. But to assess this possibility it is necessary to be certain about the diagnosis. In fairness it should be emphasized that, in many of the patients described, the diagnosis would probably be agreed by all workers, but doubt exists about cases with mixed diagnosis such as combined deficiencies of factors VIII and IX and about families which include more than one type of defect in different members.

Cutaneous Innervation: Proceedings of the Brown University Symposium on the Biology of Skin, 1959
Vol 1 of Advances in Biology of Skin
edited by William Montagna
pp xii+203 illustrated 63s.
Oxford &c: Pergamon Press (Symposium Publications Division) 1960

For some years the Brown University of Rhode Island has held a series of very interesting symposia dealing with various aspects and problems relating to the biology of the skin but, until the production of this book, the proceedings have not been published. The editor maintained that the nature of the informal discussions which accompanied the presentation of the papers was such as to make the recording difficult but this has now been overcome by inviting the authors to incorporate in their contributions important points which were introduced in the discussions.

The book is composed of nine chapters, each written by an eminent authority in his particular field, the whole dealing with cutaneous innervation. The first chapter covers, very thoroughly, the pattern of cutaneous innervation of the human skin, the second deals with similarities in cutaneous nerve endings. Others cover the ground of autonomic innervation, cholesterinases in the nerves, relationship of nerve-fibre size to modality of sensation and the central paths of afferent sensory impulses. Weddell, well known for his contributions in this field, submits an excellent study of the mechanism of common sensibility and there is another chapter on the structures and processes involved in the sensation of itch. Finally, Rothman has added a short and stimulating contribution on the patho-physiology of itch sensation though this subject is also dealt with in other chapters.

This book, which is profusely and admirably illustrated, can be strongly recommended to dermatologists who wish to be well informed in this interesting and important field.

Journal of Theoretical Biology
Vol 1 No 1 January 1961
pp 106 illustrated 121s per annum
London & New York: Academic Press 1961

Of the new journals that are now proliferating, not all justify their foundation. The *Journal of Theoretical Biology*, however, must surely receive an unequivocal welcome because it deals not with a subsection of a specialty but with subject matter whose publication elsewhere might prove difficult. It has been established as a central international medium for theoretical work in all fields of biology and contributors are not expected to support their arguments with new results. This contrasts with the traditional view that speculation beyond the limits of experimental data is undesirable. It is demonstrable, however, that striking advances in knowledge may follow the formulation of a hypothesis, experimental proof of which is not found until later. Such instances are commonplace in the physical sciences. In biology an outstanding example of recent times is the prediction of immunological tolerance and its subsequent demonstration with the aid of the homograft reaction.

Because theory is now tending to outstrip experimental observations in biology, the first issue of the Journal provides an interesting picture of some of the potential lines of advance. The Chief Editor is J F Danielli.

The failure of many of the papers to incorporate a summary seems undesirable even where the paper concerned is short, and the inclusion of titles of papers in the list of references is helpful to the reader and adds little to the burdens of contributor or editor. It seems likely, that the *Journal of Theoretical Biology* will have a long and distinguished future.

Protection Against Radiation
by John D Abbatt MB ChB DMR, J R A Labey PhD BSc AInstP and D J Matthias
pp viii+235 illustrated 25s
London: Cassell 1961

This book deals with the physical and biochemical aspects of radioactivity, and with methods of measuring and recording dose. It is clearly written, pleasant to read and accurate. It will become a standard textbook for all who study radiation problems.

It is difficult to justify the sub-title 'A Practical Handbook'. This will mislead the diagnostic

radiologist, for the book contains very little practical information about how to reduce the dose to patients and staff in hospital. The book would have wider application if the authors would consider this problem in a subsequent edition. They fully justify their statement that the 'essential prerequisite of any protection is awareness of the nature of the hazard and of exposure to that hazard'.

Northern Rhodesia in the Days of the Charter: A Medical and Social Study 1878–1924
by Michael Gelfand CBE MD FRCP
pp xvii+291 illustrated 30s
Oxford: Basil Blackwell 1961

Dr Gelfand's study deals primarily with social welfare and medical problems in Northern Rhodesia from 1878 until the British South Africa Company handed over to the Colonial Office in 1924.

The first European missionaries, the Jesuits, came to a land ravaged by disease and lacking all medical services; but in the end they were vanquished by malaria and blackwater fever. They were followed by the Protestants who – although many were carried off by fever – fared better because of more careful attention to regular dosage with quinine.

When the Company took control, they provided rudimentary medical services for both Europeans and Africans, including cottage hospitals with a trained nurse in charge, in the larger centres. Later the Administration employed increasing numbers of medical officers as hygiene specialists and efficient hospitals, staffed by European sisters, were established in the towns.

The greatest curse of the country, however, was the slave trade. A chief would raid some village, carry off the inhabitants and then Arab dealers herded them to the coast, many of the miserable wretches perishing on the way. A slave could be purchased for about 100 yards of calico, and two or more for a good gun. By 1903 the export of slaves had been stamped out by force; but domestic slavery among the Africans lingered on until the First World War.

To-day when the fashion is to denounce 'colonialism' it is illuminating to learn how Europeans strove to bring health and justice to a primitive country, often at the cost of their own lives.

Atlas of Anatomy and Surgical Approaches in Orthopædic Surgery – Lower Extremity
by Rodolfo Cosentino MD
Vol 2 pp vii+263 illustrated £5 12s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications 1960

This Atlas is based upon dissections of the cadaver, and consists of 139 full-page illustrations with brief anatomical notes. Much of the material follows a familiar plan of anatomical display, layer by layer, and relatively little space is devoted to the details of surgical approach. There are a few photographs which illustrate the sites of skin incisions and a section dealing with some approaches to the hip-joint but there is little to excite or stimulate the surgeon, whose approach is inevitably a regional one.

The illustrations throughout are of a high order, particularly of the thigh and of the foot, and with the aid of a somewhat limited text, give a good anatomical review of the region. It is doubtful if an operative exposure can ever usefully be shown upon the cadaver and the illustrations in this book certainly stress the weakness of the method. Anatomical relationships are often changed by limb position, which in itself adds so much to exposure in surgery that one would like to see much more space devoted to the anatomy of the living subject. It is perhaps a comment on the present emphasis on teaching that this book by a surgeon should use the cadaver for its illustrations whilst so many anatomists are looking for a dynamic approach as the basis of modern anatomical teaching.

Molecular Genetics and Human Disease
edited by Lytt I Gardner MD
pp xvii+297 illustrated 92s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications 1961

The progress in human genetics during the past decade has been spectacular. Ten years ago we knew little about inherited human diseases apart from the fact that they followed Mendelian rules. The basic biochemical lesions in a wide range of conditions have since been identified, and in some instances we know the underlying defects in protein structure resulting from gene mutations. Some of the highlights were reviewed by various contributors to a symposium held in the Department of Pediatrics, State University, New York, in 1960 and now published as the present volume.

Childs shows how Garrod's prognostication that gene defects will often be associated with abnormalities in particular enzymes has been fully borne out. Two examples are discussed in detail by other authors: deficiency of galactose-1-phosphate uridyl transferase in galactosæmia, and deficiency of glucose-6-phosphate dehydrogenase which makes red cells susceptible to hæmolysis by primaquine and other agents. Background information on macromolecular structure is provided by Crick, who reviews the replication of deoxyribonucleic acid, and Ingram, who describes how several mutations produce single amino-acid substitutions in hæmoglobin half-molecules.

Chromosomal aberrations associated with disease are reviewed by several authors. In addition to the now well-known trisomy of chromosome 21 in mongolism and the XXY and XO constitutions in Klinefelter's and Turner's syndromes, a number of rare abnormalities associated with unusual chromosome constitutions have been reported. Estimations of mutation rates in the mouse, and the difficulties associated with extrapolation of these results to man, are discussed in some detail.

The contributions in this volume are not meant to be comprehensive, and most of the material has been presented more fully elsewhere. The volume is nevertheless well produced, illustrated, and indexed, which allows easy and pleasant reading.

Clinicopathological Conferences of the Massachusetts General Hospital: Selected Medical Cases
by Benjamin Castleman MD and H Robert Dudley jr MD
pp xiv+295 illustrated 90s
London: J & A Churchill Ltd 1961

Of the many contributions to medicine from the Massachusetts General Hospital, the Clinicopathological Conference is not the least. The idea of this novel method of medical teaching arose in the mind of Walter B Cannon. This practical application we owe to Richard C Cabot, who in 1900 began to use a simplified C.P.C. technique in teaching his students. The modern C.P.C., with the participation of the pathologist, dates from 1910. Needless to say, fashions have changed in the past fifty years. Formerly any case of subacute bacterial endocarditis would have been considered suitable for discussion, but now only cases with unusual features would be deemed worthy of inclusion.

The present volume consists of 50 case reports selected as being of clinical interest, as illustrating current bedside and laboratory techniques, and in some instances as being of historical interest. All have been published in the *New England Journal of Medicine* during the past twenty-five years. As might be expected many of the patients suffered from 'difficult' diseases, such as obscure carcinomata, disseminated lupus erythematosus, carcinoid tumours, systemic amyloidosis and dermatomyositis, but all have some message for the clinician.

Many of the case reports have addenda, written up to twenty-four years later. In some cases, the diagnosis would have been no easier to-day, in others surprised comment is made at the solver's lack of, or even disregard of, laboratory investigations, and in some the diagnosis has been altered in the light of modern knowledge.

This is a beautifully produced book, at once attractive and instructive.

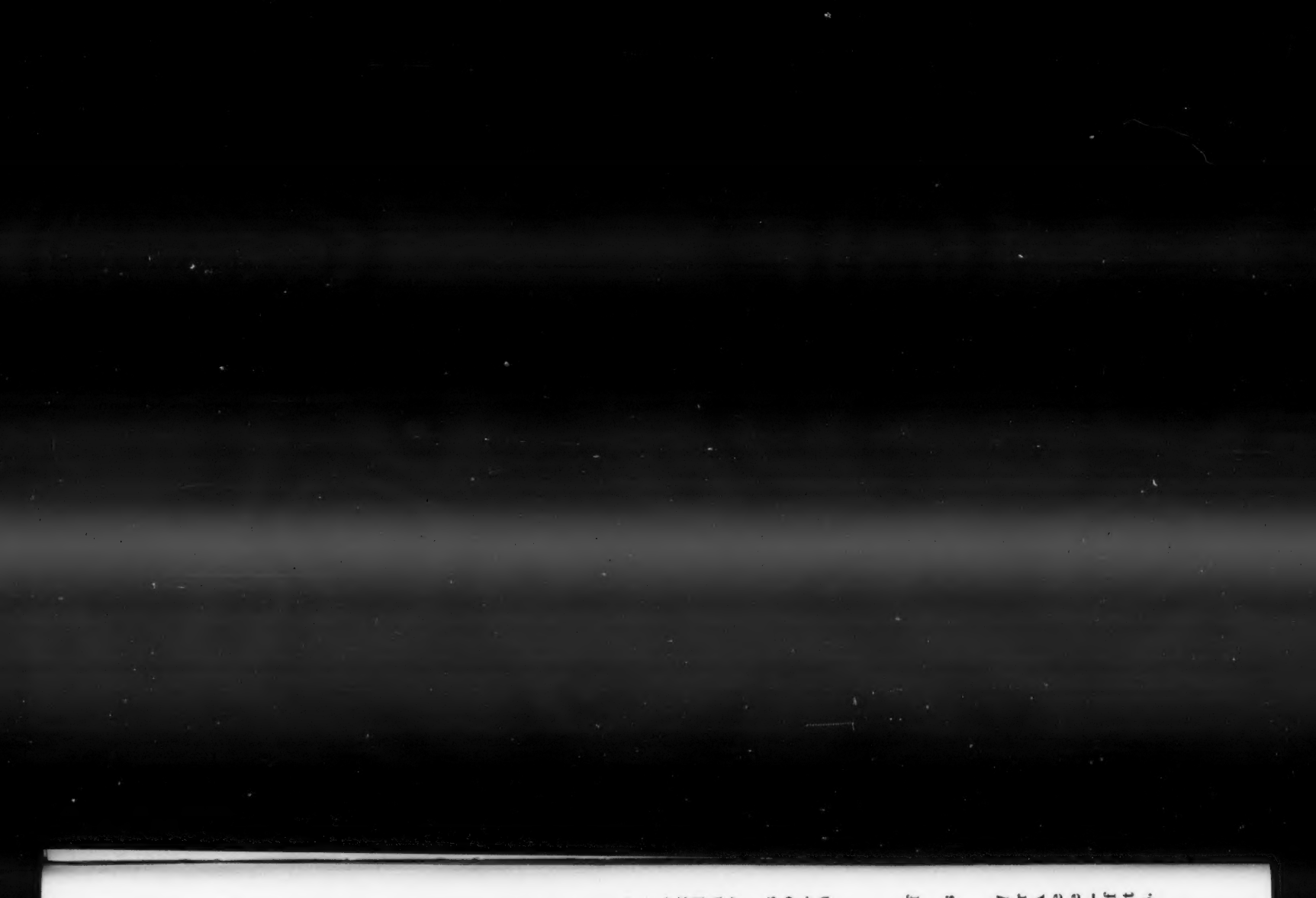
Gynäkologische Urologie
by W Langreder
pp xii+306 illustrated DM 59
Stuttgart: Georg Thieme Verlag 1961

As the gynæcologist-obstetrician is becoming increasingly aware of the fundamental importance of urology in the practice of his specialty, a contribution such as Professor Langreder sets out to make is to be welcomed.

Unfortunately, the author has failed to define the limits of 'gynæcological urology', so that he dwells in considerable detail on urological problems quite beyond the scope of the gynæcologist. For example, primary vesical neoplasms are unlikely to present by gynæcological symptomatology. Paradoxically, secondary bladder-deposits due to cancer of the cervix receive scant attention, although anterior or total pelvic exenteration has become an established gynæcological procedure.

On certain more fundamental problems, the author is evasive or vague: within the framework of a book such as this, it may not be possible to enter fully into the subject of toxæmia of pregnancy, but to allude to it as the condition of 'a thousand theories' is to evade the issue. Regarding anuria, the existence of various types of artificial kidney is common knowledge, but precisely when to invoke its aid is probably not, and could very usefully have been discussed in detail.

In the section on stress incontinence, which is good, Mulvany's operation is wrongly stated to be a vaginal procedure. His papers are not referred to in the bibliography, which is poor. In summary, the book is disappointing.

Surgery is Destined to the Practice of Medicine
Hunterian Oration Royal College of Surgeons of England
by Sir Reginald Watson-Jones BSC MCh FRCS FRACS (HON) FRSCE (HON) FACS (HON)
pp 81 illustrated 21s.
Edinburgh & London: E & S Livingstone Ltd 1961

This beautifully produced volume records Sir Reginald Watson-Jones' Hunterian oration. A list of all the previous Hunterian orators and the titles of their lectures is given and there are some fine illustrations of Hunteriana. There is a fascinating account of the change in the pattern of orthopædic surgery in recent years laying great stress on conservative and preventative measures.